Official Title: Phase III, Randomized, Multicenter Double-Blind, Double Dummy 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

NCT Number: NCT02136069

Document Date: Protocol Amendment Version 7: 22-October-2018

PROTOCOL

TITLE:	**PHASE III, RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY 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**
PROTOCOL NUMBER:	GA29103
VERSION NUMBER:	7
EUDRACT NUMBER:	2013-004282-14
IND NUMBER:	100366
TEST PRODUCT:	Etrolizumab (PRO145223, RO5490261)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 21 January 2014
DATES AMENDED:	Version 2: 26 March 2014 Version 3: 9 July 2014 Version 4: 5 October 2015 Version 5: 2 November 2016 Version 6: 25 January 2018 Version 7: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	22-Oct-2018 19:15:38

PROTOCOL AMENDMENT, VERSION 7: RATIONALE

Protocol GA29103 has been amended primarily to reflect an increase in the assumed difference in treatment effect between etrolizumab and infliximab; as such, the study sample size has been reduced. This and other changes to the protocol, along with a rationale for each change, are summarized below:

- The difference in treatment effect between etrolizumab and infliximab is considered to be higher than previously assumed. As a result, the estimated sample size for this study has been reduced from 600 to 390 patients. Patients will continue to be randomized in the same 1:1 ratio. (Sections 3.1.1, 3.1.1.4, 6.1, and 9.4, and Figure 1).

Additional changes are 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 1.1, 1.2, and 1.3).
- A secondary efficacy endpoint, to evaluate clinical remission at Week 54 among patients with a clinical response at Week 10, has been added (Sections 2.1, 3.4.1, 6.4.2).
- Language has been amended to clarify exploratory biomarker analyses (Sections 2.4, 3.3.4, 3.4.4, 4.7.1.5, and 6.6).
- Language has been added to clarify that an endoscopy for the documentation of disease activity may be performed at the discretion of the investigator for patients exiting the treatment period early for any reason (Sections 3.1.1.2 and 4.4.2.3, and Appendix 1).
- Janus kinase inhibitors have been added to the list of rescue therapies prohibited at any time during the study (Sections 3.1.1.2, 4.4.2.3, and 4.5.2).
- Language has been updated to indicate that additional biomarkers including, but not limited to, protein biomarkers or mRNA gene expression will be assessed at baseline and after treatment to increase the knowledge and understanding of disease biology, patient populations, etrolizumab mechanism of action and relationships to exposure, and inform biomarkers predictive of response to treatment (Section 3.3.4).
- Exclusion criteria have been amended to include any treatment with tofacitinib during screening as this drug has been approved for use in the United States and European Union and is no longer an investigational product (Section 4.1.2).
- Information regarding the reporting of adverse events related to medical device complaints in individuals other than the study patient has been added in Section 4.4.6.

- Procedures for adverse event reporting have been updated to clarify that adverse event reports will not be derived from patient-reported outcome (PRO) data and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events (Section 5.3.5.12).
- Appendix 4 has been updated to clarify that for patients undergoing re-screening who meet the criteria to waive the endoscopy, the MCS rectal bleeding and stool frequency subscores will be derived from the 3 consecutive days prior to the new enrollment day.

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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**PHASE III, RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY 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**
PROTOCOL NUMBER:	GA29103
VERSION NUMBER:	7
EUDRACT NUMBER:	2013-004282-14
IND NUMBER:	100366
TEST PRODUCT:	Etrolizumab (PRO145223, RO5490261)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**PHASE III, RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY 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**
PROTOCOL NUMBER:	GA29103
VERSION NUMBER:	7
EUDRACT NUMBER:	2013-004282-14
IND NUMBER:	100366
TEST PRODUCT:	Etrolizumab (PRO145223, RO5490261)
PHASE:	III
INDICATION:	Ulcerative colitis
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of etrolizumab (105 mg subcutaneous [SC] every 4 weeks [Q4W]) compared with infliximab in achieving both clinical response at Week 10 and clinical remission at Week 54 in patients with ulcerative colitis (UC) as determined by the Mayo Clinic Score (MCS).

Secondary efficacy objectives for this study are as follows:

- To evaluate clinical remission at Week 10
- To evaluate clinical remission at Week 54
- To evaluate clinical remission achieved at both Week 10 and Week 54
- *To evaluate clinical remission at Week 54 among patients with a clinical response at Week 10*
- To evaluate improvement in endoscopic appearance of the mucosa at Week 10
- To evaluate improvement in endoscopic appearance of the mucosa at Week 54
- To evaluate improvement in endoscopic appearance of the mucosa achieved at both Week 10 and Week 54
- To evaluate endoscopic remission at Week 54
- To evaluate clinical response at Week 10
- To evaluate clinical response achieved at both Week 10 and Week 54
- To evaluate corticosteroid-free clinical remission at Week 54 (off corticosteroids for at least 24 weeks prior to Week 54) in patients who were receiving corticosteroids at baseline

- To evaluate change from baseline in patient-reported health-related quality of life (QOL) at Weeks 10, 30, and 54, as assessed by the Inflammatory Bowel Disease Questionnaire (IBDQ)

The exploratory efficacy objectives for this study are as follows:

- To evaluate remission at Week 10
- To evaluate remission at Week 54
- To evaluate remission at both Week 10 and Week 54
- To evaluate change in health utilities, as assessed by the EuroQoL Five-Dimension Questionnaire (EQ-5D), from baseline to Weeks 10, 30, and 54
- To evaluate the frequency and duration of hospitalizations from baseline to Week 54

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the overall safety and tolerability of etrolizumab over a period of 54 weeks
- 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) to etrolizumab, or if necessary, infliximab

Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives for this study are as follows:

- To evaluate the etrolizumab serum concentration at the time of primary endpoint evaluation and at a predose timepoint (Week 12)
- To evaluate the interindividual variability of and potential covariate effects on etrolizumab (or potentially infliximab) serum exposure

Exploratory Pharmacodynamic, *Predictive, and Prognostic* Objectives

The exploratory pharmacodynamics (PD)*, predictive, and prognostic* objectives for this study are as follows:

- To evaluate the relationship between baseline colonic mucosal and/or peripheral blood biomarkers, including, but not limited to, αE integrin, and response to study treatment
- To evaluate the *expression* levels of biomarkers in colonic tissue and/or peripheral blood, including, but not limited to, αE integrin, at baseline and during the treatment period
- To evaluate the PD effects on biomarkers in stool samples through assessments that may include, but are not limited to, analyses of the microbiota and bacterial cultures at baseline and during the treatment period

Study Design

Description of Study

This is a multicenter, Phase III, randomized, double-blind, double-dummy, parallel-group study to evaluate the safety, efficacy, and tolerability of etrolizumab (105 mg SC Q4W) compared with infliximab (5 mg/kg intravenous [IV] Weeks 0, 2, and 6, then every 8 weeks [Q8W]) in the treatment of moderate to severe UC.

Patients enrolled in this study may be eligible to participate in an open-label extension and safety monitoring (OLE-SM) study (GA28951), which consists of two parts: Part 1 (designated OLE [open-label extension]) and Part 2 (designated SM [safety monitoring]).

Disease activity will be measured using the MCS, which is the current outcome measure accepted by regulatory authorities for drug development in UC. The target population consists of patients with moderately to severely active UC (defined as MCS of 6–12, endoscopy subscore of ≥ 2, as determined by the central reading procedure described in protocol, a rectal bleeding subscore ≥ 1, and a stool frequency subscore ≥ 1) and involvement that extends a minimum of 20 cm from the anal verge.

All patients are to be naive to tumor necrosis factor (TNF) inhibitors.

Patients must have had an inadequate response, loss of response, or intolerance to prior immunosuppressant and/or corticosteroid treatment.

Patients who are on background immunosuppressant therapy (6-MP, AZA, MTX) may be enrolled if they have received a stable dose for at least 8 weeks prior to randomization (Day 1). Such patients should continue on their stable baseline doses of their background immunosuppressant therapy throughout the study unless dose reduction or discontinuation is required due to toxicity. 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 remains at the discretion of the investigator.

Patients on oral corticosteroid therapy (prednisone at a stable dose of ≤ 30 mg, or equivalent) may be enrolled according to the following criteria:

- If corticosteroid therapy is ongoing or has just been initiated, the dose has to be stable for at least 4 weeks immediately prior to randomization (Day 1)
- If corticosteroids are being tapered, the dose has to be stable for 2 weeks immediately prior to randomization (Day 1)

Such patients should continue stable doses of their background corticosteroid until Week 10, at which point a corticosteroid taper will be initiated for all patients entering the Maintenance Phase.

Initiation of corticosteroid or an increase in corticosteroid dose above the patients' entry dose (up to a maximum of 30 mg/day of prednisone [or equivalent]) will not be permitted during screening. Use of budesonide will be allowed at stable doses (≤ 9 mg) provided that the dose has been stable for ≥ 4 weeks prior to randomization (Day 1). Oral 5-aminosalicylate (5-ASA) treatment and probiotics for the treatment of UC may be continued at a stable dose as long as the dose(s) had been stable for ≥ 4 weeks and ≥ 2 weeks, respectively, prior to randomization (Day 1). Certain concomitant treatments are prohibited (see protocol for list of all prohibited concomitant treatments).

Patients must have discontinued topical treatments for UC at least 2 weeks prior to randomization (Day 1).

The study will be divided into:

- Screening period of up to 35 days (for details see protocol)
- Double-blind treatment period of 54 weeks, composed of an Induction Phase (up to Week 10) and a Maintenance Phase (Week 10 to Week 54)
- Safety follow-up period of 12 weeks.

A total of approximately 390 patients will be recruited from approximately 200 sites. Patients will be stratified by concomitant treatment with corticosteroids (including budesonide) at baseline (yes/no), concomitant treatment with immunosuppressants at baseline (yes/no), and baseline disease activity as measured during screening (MCS ≤ 9 vs. MCS ≥ 10).

Patients completing the Maintenance Phase at Week 54, patients identified as having disease worsening between Weeks 10 and 54, or patients who receive defined rescue medication(s) may enroll in Part 1 (OLE) of Study GA28951, if eligible, where they will receive open-label etrolizumab after a brief washout phase. If they do not enroll in Part 1 (OLE) of Study GA28951, they will enter the 12-week safety follow-up period of this study and will then be requested to enroll in Part 2 (SM) of Study GA28951 for 92 weeks of extended PML monitoring.

Study Drug Administration

Following screening, patients will be randomized in a 1:1 ratio to receive 105 mg etrolizumab or 5 mg/kg infliximab. The study design is double-blind, double-dummy, so all patients will receive two study treatments, either active etrolizumab + infliximab dummy or active infliximab + etrolizumab dummy. The dummy for etrolizumab will be a matched SC placebo, whereas the dummy for infliximab will be an IV saline infusion. Patients will receive either 105 mg etrolizumab or etrolizumab dummy by SC administration Q4W until Week 52. Infliximab will be administered by IV infusion at Weeks 0, 2, and 6, then Q8W until Week 46. Consequently, administration of SC study medication and IV study medication occurs at different timepoints throughout the study.

The first 2 doses of etrolizumab/etrolizumab dummy will be administered via a prefilled syringe (PFS) by a health care professional (HCP) in the clinic. The subsequent two doses will be self-administered by the patient or administered by his or her caregiver in the clinic and monitored by the HCP.

If deemed appropriate by HCP, the remaining doses of etrolizumab/etrolizumab dummy study drug, starting at Week 16, will be self-administered by the patient or administered by his or her caregiver at home Q4W (action to be taken as a result of a hypersensitivity reaction provided in the protocol). On occasions when the patient has to attend the clinic the same day as an etrolizumab/etrolizumab dummy administration, the administration of study medication by the patient or his or her caregiver will occur at home after his or her study assessments in the clinic setting. If necessary, patients or their HCPs may choose to continue administration of study medication in the clinic. The details of study medication administration are provided in the protocol.

In addition, patients will receive either infliximab (5 mg/kg IV at Weeks 0, 2, and 6, then Q8W) or infliximab dummy (saline) IV at the same timepoints, administered in the clinic setting until Week 46.

Number of Patients

A total of approximately 390 patients will be enrolled in this study from approximately 200 sites.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Able and willing to provide written informed consent
- 18–80 years of age, inclusive
- Diagnosis of UC established at least 3 months prior to randomization (Day 1) by clinical and endoscopic evidence. This diagnosis should be corroborated by histopathology conducted at any time prior to screening and documented by a histopathology report. (Note: histopathology may be performed at screening, if no prior report is readily available.)
- Moderately to severely active UC as determined by an MCS of 6–12, with an endoscopic subscore ≥ 2 as determined by the central reading procedure, a rectal bleeding subscore ≥ 1, and a stool frequency subscore ≥ 1 during the screening period (prior to randomization [Day 1]). See also the protocol for additional information regarding this time window.
- Evidence of UC extending a minimum of 20 cm from the anal verge as determined by baseline endoscopy (flexible sigmoidoscopy or colonoscopy) performed during screening, 4–16 days prior to randomization (Day 1). See also the protocol for additional information regarding this time window.
- Naive to treatment with any TNF inhibitor therapy (including TNF inhibitor biosimilars)

- Patients must have had an inadequate response, loss of response, or intolerance to prior immunosuppressant and/or corticosteroid treatment.

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

  Persistent signs and symptoms of active disease despite a history of at least one 12-week regimen of oral AZA (≥ 1.5 mg/kg) or 6-MP (≥ 0.75 mg/kg) and/or MTX (≥ 15 mg/week) within the previous 5 years

  Persistent signs and symptoms of active disease despite a 6-TG level of ≥ 230 pmol/8 $\times$ 108 RBCs during at least one 12-week regimen of oral AZA or 6-MP at a stable or increasing dose within the previous 5 years(or equivalent)

  History of intolerance to AZA, 6-MP, or MTX (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, LFT abnormalities, lymphopenia, *TPMT* genetic mutation, infection) within the previous 5 years

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

  Steroid refractory: persistent symptoms of active disease despite treatment with at least one 4-week induction regimen that included a dose of ≥ 30 mg prednisone (oral) daily (or equivalent) for at least 2 weeks or IV for at least 1 week within the previous 5 years

  Steroid dependent: two failed attempts to taper steroids below a dose equivalent to 10 mg prednisone (oral) daily

  Steroid intolerant: history of intolerance to corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection) within the previous 5 years

- Any ongoing UC therapy must be at stable doses:

  May be receiving oral 5-ASA compounds provided that the dose has been stable for ≥ 4 weeks immediately prior to randomization (Day 1)

  May be receiving oral corticosteroid therapy (prednisone at a stable dose of ≤ 30 mg a day, or equivalent steroid)

  If corticosteroid therapy is ongoing or has recently been initiated, the dose has to be stable for at least 4 weeks immediately prior to randomization (Day 1). If corticosteroids are being tapered, the dose has to be stable for at least 2 weeks immediately prior to randomization.

  May be receiving budesonide therapy at a stable dose of up to 9 mg a day for ≥ 4 weeks prior to randomization (Day 1)

  May be receiving probiotics (e.g., Culturelle, *Saccharomyces boulardii*), provided that the dose has been stable for ≥ 2 weeks immediately prior to randomization (Day 1)

  May be receiving AZA, 6-MP, or MTX, provided that the dose has been stable for ≥ 8 weeks immediately prior to randomization (Day 1)

- For women who are not postmenopausal (at least 12 months of non–therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or 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.
- Must have received a colonoscopy within the past year or be willing to undergo a colonoscopy in lieu of a flexible sigmoidoscopy at screening. This colonoscopy must:

  Confirm disease extent (defined as 1) left-sided colitis [up to the splenic flexure], 2) extensive colitis [beyond the splenic flexure but not involving the entire colon], and 3) pancolitis)

  Include removal of any adenomatous polyps

  Document evidence of surveillance for dysplasia for all patients with left-sided colitis of >12 years' duration and total/extensive colitis of >8 years' duration

<u>Exclusion Criteria</u>

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

Exclusion Criteria Related to Inflammatory Bowel Disease

- Prior extensive colonic resection, subtotal or total colectomy, or planned surgery for UC
- Past or present ileostomy or colostomy
- Diagnosis of indeterminate colitis
- Suspicion of ischemic colitis, radiation colitis, or microscopic colitis
- Diagnosis of toxic megacolon within 12 months of initial screening visit
- Any diagnosis of Crohn's disease
- Past or present fistula or abdominal abscess
- A history or current evidence of colonic mucosal dysplasia
- Patients with any stricture (stenosis) of the colon
- Patients with history or evidence of adenomatous colonic polyps that have not been removed

Exclusion Criteria Related to Prior or Concomitant Therapy

- Any prior treatment with etrolizumab or other anti-integrin agents (including natalizumab, vedolizumab, and efalizumab)
- Any prior treatment with anti-adhesion molecules (e.g., anti-MAdCAM-1)
- Any prior treatment with rituximab
- *Any treatment with tofacitinib during screening*
- Use of IV steroids within 30 days prior to screening with the exception of a single administration of IV steroid
- Use of agents that deplete B or T cells (e.g., alemtuzumab or visilizumab) within 12 months prior to randomization (Day 1), with the exception of AZA and 6-MP
- Use of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) within 4 weeks prior to randomization (Day 1)
- Chronic nonsteroidal anti-inflammatory drug (NSAID) use (Note that occasional use of NSAIDs and acetaminophen [e.g., headache, arthritis, myalgias, or menstrual cramps] and aspirin up to 325 mg daily is permitted.)

- Patients who are currently using anticoagulants including, but not limited to, warfarin, heparin, enoxaparin, dabigatran, apixaban, rivaroxaban. (Note that antiplatelet agents such as aspirin up to 325 mg daily or clopidogrel are permitted.)
- Patients who have received treatment with corticosteroid enemas/suppositories and/or topical (rectal) 5-ASA preparations within 2 weeks prior to randomization (Day 1)
- Apheresis (i.e., Adacolumn apheresis) within 2 weeks prior to randomization (Day 1)
- Received any investigational treatment including investigational vaccines within 5 half-lives of the investigational product or 28 days after the last dose (whichever is greater) prior to randomization (Day 1) of the study
- History of moderate or severe allergic or anaphylactic/anaphylactoid reactions to chimeric, human, or humanized antibodies, fusion proteins, or murine proteins or hypersensitivity to etrolizumab (active drug substance) or any of the excipients (L-histidine, L-arginine, succinic acid, polysorbate 20)
- Patients administered tube feeding, defined formula diets, or parenteral alimentation/nutrition who have not discontinued these treatments ≥ 3 weeks prior to randomization (Day 1)

Exclusion Criteria Related to General Safety

- Pregnant or lactating
- Lack of peripheral venous access
- Hospitalized (other than for elective reasons) during the screening period
- Inability to comply with study protocol, in the opinion of the investigator
- Significant uncontrolled comorbidity, such as cardiac (e.g., moderate to severe heart failure New York Heart Association [NYHA] Class III/IV), pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders (excluding UC)
- Neurologic conditions or diseases that may interfere with monitoring for PML
- History of demyelinating disease
- Clinically significant abnormalities on screening neurologic examination (PML Objective Checklist)
- Clinically significant abnormalities on the screening PML Subjective Checklist
- History of alcohol, drug, or chemical abuse ≤ 6 months prior to screening
- Conditions other than UC that could require treatment with > 10 mg/day of prednisone (or equivalent) during the course of the study
- History of cancer, including hematologic malignancy, solid tumors, and carcinoma in situ, within 5 years before screening with the following exceptions:

  Local basal or squamous cell carcinoma of the skin that has been excised and is considered cured is not exclusionary.

  A history of chronic myelogenous leukemia, hairy cell leukemia, melanoma, renal cell carcinoma, or Kaposi sarcoma is exclusionary irrespective of the duration of time before screening.

  History of a cervical smear indicating the presence of adenocarcinoma in situ (AIS), high-grade squamous intraepithelial lesions (HSIL), or cervical intraepithelial neoplasia (CIN) of Grade > 1, is exclusionary irrespective of the duration of time before screening.

Exclusion Criteria Related to Infection Risk

- Congenital or acquired immune deficiency
- Patients must undergo screening for HIV and test positive for preliminary and confirmatory tests

- Positive hepatitis C virus (HCV) antibody test result, unless the patient (1) has undetectable HCV RNA levels for >6 months after completing a successful course of HCV anti-viral treatment and an undetectable HCV RNA at screening or (2) has a known history of HCV antibody positivity with a history of undetectable HCV RNA for >6 months and undetectable HCV RNA at screening in the absence of history of HCV anti-viral treatment.
- Patients must undergo screening for hepatitis B virus (HBV). This includes testing for HBsAg (HBV surface antigen), anti-HBc total (HBV core antibody total), and HBV DNA (patients who test negative for these tests are eligible for this study):

  Patients who test positive for surface antigen (HBsAg+) are not eligible for this study, regardless of the results of other hepatitis B tests.

  Patients who test positive only for core antibody (anti-HBc+) must undergo further testing for hepatitis B DNA (HBV DNA test).

    If the HBV DNA test result is positive, the patient is not eligible for this study.

    In the event the HBV DNA test cannot be performed, the patient is not eligible for this study.

    If the HBV DNA test is negative, the patient is eligible for this study. These patients will undergo periodic monitoring for HBV DNA during the study
- Evidence of or treatment for *Clostridium difficile* (as assessed by C. difficile toxin testing) within 60 days prior to randomization (Day 1) or other intestinal pathogens (as assessed by stool culture and ova and parasite evaluation) within 30 days prior to randomization (Day 1)
- Evidence of or treatment for clinically significant cytomegalovirus (CMV) colitis (based on the investigator's judgment) within 60 days prior to randomization (Day 1). Laboratory confirmation of CMV from a colon biopsy sample is required during screening evaluation only if clinical suspicion is high and to determine the need for CMV treatment
- History of active or latent treated tuberculosis (TB) regardless of treatment history

  Patients with a history of active or latent TB (based on a positive screening assay, either purified protein derivative [PPD] skin test or QuantiFERON®TB Gold test) are not eligible for this study.

  Patients with a chest X-ray (posteroanterior [PA] and lateral) within 3 months of enrollment suspicious for pulmonary TB are **not** eligible for this study.

  Any immunosuppressed patient with a strong suspicion of TB exposure and no prior vaccination with bacille Calmette-Guérin (BCG) should be considered at risk for having latent TB infection.

  Patients at risk for TB exposure include:

    Patients who have household contact with a person with active TB

    Patients living in areas with high incidence of TB

    Patients who frequently visit areas with high prevalence of active TB

  Patients who meet these criteria should be evaluated per local practice to exclude latent TB.
- History of recurrent opportunistic infections and/or history of severe disseminated viral infections (e.g., herpes)
- Any serious opportunistic infection within the last 6 months
- Any current or recent signs or symptoms (within 4 weeks before screening and during screening) of infection, except for the following:

  Minor infections (e.g., common cold) that have, in the investigator's judgment, completely resolved prior to randomization (Day 1)

  Fungal infections of the nail beds

  Oral or vaginal candidiasis that has resolved with or without treatment prior to randomization (Day 1)

- Any major episode of infection requiring treatment with IV antibiotics within 8 weeks prior to screening or oral antibiotics within 4 weeks prior to screening

  Treatment with antibiotics as adjunctive therapy for UC in the absence of documented infection is not exclusionary.
- Received a live attenuated vaccine within 4 weeks prior to randomization (Day 1)
- History of organ transplant

Exclusion Criteria Related to Laboratory Values (at Screening)

- Serum creatinine $> 2 \times$ upper limit of normal (ULN)
- ALT or AST $> 3 \times$ ULN or alkaline phosphatase $> 3 \times$ ULN or total bilirubin $> 2.5 \times$ ULN (unconjugated hyperbilirubinemia that is associated with known Gilbert's syndrome is not an exclusion criterion)
- Platelet count $< 100{,}000/\mu L$
- Hemoglobin < 8 g/dL
- Absolute neutrophil count $< 1500/\mu L$
- Absolute lymphocyte count $< 500/\mu L$

Length of Study

The total length of the treatment period will be 54 weeks. Patients who have disease worsening between Weeks 10 and 54, patients who receive defined rescue treatment(s), and patients who complete 54 weeks of the study may be given the option of enrolling in the Part 1 (OLE) of Study GA28951, where they will receive open-label etrolizumab treatment.

Those who do not enroll in Part 1 (OLE) of Study GA28951 will continue to 12 weeks of safety follow-up in this protocol (without the washout phase) and then be requested to enroll in Part 2 (SM) of Study GA28951 for 92 weeks of PML monitoring.

The total length of the study is expected to last from the first patient screened to either the last patient in last safety follow-up visit in this protocol or the last patient enrolled into Study GA28951, whichever is later.

End of Study

The end of the study is defined as the last patient last safety follow-up visit in this protocol, or last patient in this protocol enrolled in Study GA28951, whichever is later.

Outcome Measures

Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

Primary Efficacy Outcome Measure

- Both clinical response at Week 10 and clinical remission at Week 54 in patients with UC as determined by the MCS

Secondary Efficacy Outcome Measures

- Clinical remission at Week 10
- Clinical remission at Week 54
- Clinical remission achieved at both Week 10 and Week 54
- *Clinical remission at Week 54 among patients with a clinical response at Week 10*
- Improvement in endoscopic appearance of the mucosa at Week 10
- Improvement in endoscopic appearance of the mucosa at Week 54
- Improvement in endoscopic appearance of the mucosa achieved at both Week 10 and Week 54
- Endoscopic remission Week 54
- Clinical response at Week 10

- Clinical response achieved at both Week 10 and Week 54
- Corticosteroid-free clinical remission at Week 54 (off corticosteroids for at least 24 weeks prior to Week 54) in patients who were receiving corticosteroids at baseline
- Change from baseline in patient-reported health-related QOL at Weeks 10, 30, and 54 as assessed by the IBDQ

Exploratory Efficacy Outcome Measures

- Remission at Week 10
- Remission at Week 54
- Remission at both Week 10 and Week 54
- Change in health utilities, as assessed by the EQ-5D, from baseline to Weeks 10, 30, and 54
- Frequency and duration of hospitalizations from baseline to Week 54

Safety Outcome Measures

The safety outcome measures for 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 study drug discontinuation
- Incidence of laboratory abnormalities
- Incidence of malignancies
- Incidence of ATAs to etrolizumab, or if necessary, infliximab
- Incidence and severity of hypersensitivity reaction events

Pharmacokinetic Outcome Measures

The etrolizumab PK assessment will be performed in a subset of etrolizumab-treated patients. The PK outcome measures for this study are as follows:

- Serum concentration 2 weeks after the first dose and at steady state during the dosing period from Week 12 to Week 54
- Serum concentration at timepoints (Weeks 10, 30, and 54)

Exploratory Biomarker Outcome Measures

The exploratory biomarker outcome measures for this study are as follows:

- Relationship between remission and baseline levels of colonic tissue biomarkers and/or peripheral blood including, but not limited to, αE integrin. *These may be outcomes predictive or prognostic of response.*
- Changes in stool biomarkers, which may include, but are not limited to, those in the microbiota and bacterial cultures, during the Induction and Maintenance Phases as compared to baseline

Investigational Medicinal Products

Test Product

Etrolizumab PFS: containing SC formulation, 105 mg given as 0.7 mL of a 150-mg/mL solution will be administered by SC injection Q4W.

Comparator

Infliximab, 5 mg/kg IV Weeks 0, 2, and 6, then Q8W. Each infliximab vial contains 100 mg of lyophilized infliximab antibody in a 20-mL vial for IV use. An unblinded pharmacist will reconstitute and then dilute the infliximab to a dose of 5 mg/kg and a total volume of 250 mL with sterile 0.9% sodium chloride for infusion.

Non-Investigational Medicinal Products

Patients are to continue on their baseline dose of corticosteroid (including budesonide) to the end of the Induction Phase (Week 10). Tapering of corticosteroid (including budesonide) is to be attempted during the Maintenance Phase (Week 10 to Week 54).

Immunosuppressants (AZA, 6-MP, MTX) are to continue on the patient's baseline dose of immunosuppressant to the end of induction (Week 10) and then to continue on stable doses of immunosuppressants throughout the Maintenance Phase.

Probiotics and oral 5-ASA may be continued at a stable dose throughout the study.

Occasional use of NSAIDs and acetaminophen (e.g., headache, arthritis, myalgias, and menstrual cramps) and aspirin up to 325 mg daily are permitted throughout the study.

Anti-diarrheals (e.g., loperamide, diphenoxylate with atropine) for control of chronic diarrhea are permitted throughout the study.

Statistical Methods

Efficacy Analyses

The primary and secondary efficacy analyses will include all randomized patients who received at least one dose of study drug with patients grouped according to the treatment assigned at randomization (Day 1) (intent-to-treat [ITT] population). A per-protocol population will be defined in the Statistical Analysis Plan (SAP) for the purpose of testing for non-inferiority in induction of clinical remission at Week 10.

To manage the overall type I error, the testing of hypotheses will be performed sequentially. The primary endpoint will be tested first at an overall two-sided significance level of $\alpha = 0.05$. The testing hierarchy for the secondary endpoints will be described in the SAP.

Unless otherwise noted, analyses of efficacy outcome measures will be stratified by the stratification factors used at randomization (Day 1): baseline corticosteroids use (yes/no), baseline immunosuppressants use (yes/no), and baseline disease severity as measured during screening (MCS ≤ 9/MCS ≥ 10).

Patients who are non-evaluable for efficacy at a specific timepoint (e.g., due to missing data or early transfer to the Part 1 [OLE] of Study GA28951) will be considered non-responders for all response/remission type endpoints. In addition, initiation of an agent not allowed in combination with etrolizumab or infliximab, an immunosuppressant, oral or topical 5-ASA (up to Week 10), or corticosteroid, or increase in dose over baseline levels for treatment of worsening disease symptoms as defined in the protocol will lead to non-responder classification thereafter.

For continuous outcomes, scores after the first use of rescue medication will be imputed using the worst post-baseline score from the following assessments: the last score available prior to the start date of first rescue medication and all scores available after the start date of rescue medication use.

In addition to the analyses described in the protocol, the following analyses will be performed for the primary efficacy endpoint and key secondary efficacy endpoints. Details of these analyses will be described in the SAP:

- Sensitivity analyses to evaluate the robustness of results to the primary analysis methods (e.g., handling of dropouts)
- Subgroup analyses to evaluate the consistency of results across prespecified subgroups (e.g., based on age, sex, race/ethnicity, baseline UC medications, baseline CS dose)

Determination of Sample Size

Approximately 390 patients will be randomized in a 1:1 ratio to etrolizumab + infliximab dummy or infliximab + etrolizumab dummy. The sample size of 195 patients per group provides $approximately$ 80% power to detect a clinically meaningful difference of 12% (18% vs 30%) between the two groups for the primary endpoint, using a two-sided χ^2 test at a significance level of 0.05.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
AIS	adenocarcinoma in situ
ATA	anti-therapeutic antibody
AZA	azathioprine
BCG	bacille Calmette-Guérin
CD	Crohn's disease
CHO	Chinese hamster ovary
CIN	cervical intraepithelial neoplasia
CMV	cytomegalovirus
CRO	contract research organization
CRP	C-reactive protein
CSF	cerebrospinal fluid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ePRO	electronic patient-reported outcome
EQ-5D	EuroQoL Five-Dimension Questionnaire
FDA	U.S. Food and Drug Administration
HBsAg	HBV surface antigen
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
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council for Harmonisation
IDCC	independent data coordinating center
iDMC	independent Data Monitoring Committee
IHC	Immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board

Abbreviation	Definition
IV	Intravenous
IxRS	interactive voice/Web-based response system
JCV	John Cunningham virus
JAK	*Janus kinase*
LD	loading dose
LFT	liver function test
MAb	monoclonal antibody
MAdCAM-Fc	mucosal addressin cell adhesion molecule fragment-crystallizable region
MCS	Mayo Clinic Score
MMF	mycophenolate mofetil
MP	mercaptopurine
MRI	magnetic resonance imaging
MTX	methotrexate
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OLE	open-label extension
OLE–SM	open-label extension–safety-monitoring
PA	Posteroanterior
PD	pharmacodynamics
PEG	polyethylene glycol
PFS	prefilled syringe
PGA	Physician's Global Assessment
PK	Pharmacokinetic
pMCS	partial Mayo Clinic Score
PML	progressive multifocal leukoencephalopathy
PPD	purified protein derivative
PRO	Patient-Reported Outcome
Q4W	every 4 weeks
Q8W	every 8 weeks
QOL	quality of life
qPCR	quantitative polymerase chain reaction
RCR	Roche Clinical Repository
SAP	Statistical Analysis Plan
SC	Subcutaneous

Abbreviation	Definition
SDV	source data verification
SM	safety monitoring
SmPC	Summary of Product Characteristics
SOC	standard of care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor–alpha
TNF-IR	inadequate response to anti-tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON 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 achieve remission and prevent long-term complications would provide a valuable therapeutic option for these patients.

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-α4β7) 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 α4β7 (Holzmann et al. 1989; Hu et al. 1992) and αEβ7 (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 $\alpha 4\beta 1$ (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 $\alpha 4\beta 7$-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, 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

Although effective therapeutic options, including TNF inhibitors, are available to help patients with moderate to severe UC 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 TB, 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 [SmPC]). 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.

Etrolizumab distinguishes itself from other anti-integrins on the basis of gut selectivity combined with a dual mechanism of action. *It binds $\alpha E\beta 7$ in addition to $\alpha 4\beta 7$ and so regulates retention as well as trafficking leukocyte/lymphocyte 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 three doses in the multidose stage of the Phase I study.

A global Phase II multicenter study (Study ABS4986g; EUCALYPTUS) designed to determine the exposure-response relationship and to further characterize the safety and tolerability of etrolizumab in treatment of adult patients with moderately to severely active UC patients has been completed. Patients who had failed standard therapy and/or TNF inhibitors were randomized in a 1:1:1 ratio to receive 100 mg etrolizumab SC (0.7 mL of 150 mg/mL solution via vial and syringe, with an intended nominal dose of 100 mg) at Weeks 0, 4, and 8 or 420 mg SC at Week 0 (loading dose [LD]) followed by 300 mg SC (three injections of 0.7 mL of 150 mg/mL solution via vial and syringe, with an intended nominal dose of 300 mg) at Weeks 2, 4, and 8 (40 patients per dose arm) versus matching placebo SC (40 patients per arm). The primary objective of the study was to obtain evidence of clinical efficacy of etrolizumab as measured by induction of clinical remission (Mayo Clinic Score [MCS] ≤ 2 and no individual subscore > 1) *at Week 10 (2 weeks after the final dose)*..

Compared with patients assigned to receive placebo, patients receiving etrolizumab showed clinically meaningful efficacy for both doses: the proportion of patients in clinical remission at Week 10 was 20.5% in the 100-mg dose group and 10.3% in the 300-mg + LD group versus 0% in the placebo group ($p = 0.004$ and $p = 0.048$, respectively). In the TNF-naive subgroup, clinical remission at Week 10 was observed in 43.8% versus 0% of patients in the 100-mg etrolizumab versus placebo group, and in 25% of 300-mg + LD group. No new safety signals were observed and etrolizumab was well tolerated in the Phase II EUCALYPTUS study and in the OLE study (SPRUCE), and no events of PML have been reported to date.

Given the efficacy and safety profile demonstrated in the Phase II studies, further investigation is warranted to compare clinical remission with etrolizumab against infliximab in a previously TNF-naive population.

The present double-blinded and active-controlled study employs a robust design, utilizing independent and centrally read endoscopy to confirm patient eligibility and endpoint determination.

All patients will receive an active therapy throughout the duration of the study with ability to receive rescue therapy or enroll in an OLE study, if eligible, to receive open-label etrolizumab therapy in case of non-response or disease worsening. Patients who respond to blinded therapy may also be given the option to enroll in the OLE study at 54 weeks.

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 study.

Refer to the most recent Etrolizumab Investigator's Brochure for additional details on clinical and nonclinical studies and additional safety information.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of etrolizumab (105 mg SC every 4 weeks [Q4W]) compared with infliximab in achieving both clinical response at Week 10 and clinical remission at Week 54 in patients with UC, as determined by the MCS

Secondary efficacy objectives for this study are as follows:

- To evaluate clinical remission at Week 10
- To evaluate clinical remission at Week 54
- To evaluate clinical remission achieved at both Week 10 and Week 54
- *To evaluate clinical remission at Week 54 among patients with a clinical response at Week 10*
- To evaluate improvement in endoscopic appearance of the mucosa at Week 10
- To evaluate improvement in endoscopic appearance of the mucosa at Week 54
- To evaluate improvement in endoscopic appearance of the mucosa achieved at both Week 10 and Week 54
- To evaluate endoscopic remission at Week 54
- To evaluate clinical response at Week 10
- To evaluate clinical response achieved at both Week 10 and Week 54
- To evaluate corticosteroid-free clinical remission at Week 54 (off corticosteroids for at least 24 weeks prior to Week 54) in patients who were receiving corticosteroids at baseline
- To evaluate change from baseline in patient-reported health-related QOL at Weeks 10, 30, and 54, as assessed by the Inflammatory Bowel Disease Questionnaire (IBDQ)

The exploratory efficacy objectives for this study are as follows:

- To evaluate remission at Week 10
- To evaluate remission at Week 54
- To evaluate remission at both Week 10 and Week 54
- To evaluate change in health utilities, as assessed by the EuroQoL Five-Dimension Questionnaire (EQ-5D), from baseline to Weeks 10, 30, and 54
- To evaluate the frequency and duration of hospitalizations from baseline to Week 54

The efficacy outcomes definitions are given in Table 1.

Table 1 Efficacy Outcomes Definitions

Outcome Measure	Outcome Measure Definition
Mayo Clinic Score	MCS is a composite of 4 assessments, each rated from 0–3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment
Partial Mayo Clinic Score	pMCS is a composite of 3 assessments, each rated from 0–3: stool frequency, rectal bleeding, and physician's global assessment
Remission	MCS ≤ 2 with individual subscores ≤ 1 and a rectal bleeding subscore of 0
Clinical remission	MCS ≤ 2 with individual subscores ≤ 1
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
Composite of clinical response and clinical remission (primary outcome)	Achievement of both clinical response at Week 10 and clinical remission at Week 54
Corticosteroid-free clinical remission	Clinical remission with no corticosteroid use for 12 weeks or 24 weeks prior to Week 54
Improvement in endoscopic appearance of the mucosa	Endoscopic subscore ≤ 1
Endoscopic remission	Endoscopic subscore $= 0$

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

2.2 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the overall safety and tolerability of etrolizumab over a period of 54 weeks
- 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) to etrolizumab, or if necessary, infliximab

2.3 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objectives for this study are as follows:

- To evaluate the etrolizumab serum concentration at the time of primary endpoint evaluation and at a predose timepoint (Week 12)
- To evaluate the interindividual variability of and potential covariate effects on etrolizumab (or potentially infliximab) serum exposure

2.4 EXPLORATORY PHARMACODYNAMIC, *PREDICTIVE,* AND *PROGNOSTIC* OBJECTIVES

The exploratory pharmacodynamic (PD)*, predictive, and prognostic* objectives for this study are as follows:

- To evaluate the relationship between baseline colonic mucosal and/or peripheral blood biomarkers, including, but not limited to, αE integrin, and response to study treatment
- To evaluate the *expression* levels of biomarkers in colonic tissue and/or peripheral blood, including, but not limited to, αE integrin, at baseline and during the treatment period
- To evaluate the PD effects on biomarkers in stool samples through assessments that may include, but are not limited to, analyses of the microbiota and bacterial cultures at baseline and during the treatment period

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is a multicenter, Phase III, randomized, double-blind, double-dummy, parallel-group study to evaluate the safety, efficacy, and tolerability of etrolizumab (105 mg SC Q4W) compared with infliximab (5 mg/kg IV Weeks 0, 2, and 6, then Q8W) in the treatment of moderate to severe UC (see Figure 1).

Patients enrolled in this study may be eligible to participate in an open-label extension and safety monitoring (OLE-SM) study (GA28951), which consists of two parts: Part 1 (designated OLE [open-label extension]) and Part 2 (designated SM [safety monitoring]).

Disease activity will be measured using the MCS (see Appendix 4), which is the current outcome measure accepted by regulatory authorities for drug development in UC. The target population consists of patients with moderately to severely active UC (defined as MCS of 6–12, endoscopy subscore of ≥2, as determined by the central reading procedure described in Section 4.7.1.4, a rectal bleeding subscore ≥1, and a stool frequency subscore ≥1) and involvement that extends a minimum of 20 cm from the anal verge.

All patients are to be naive to tumor necrosis factor (TNF) inhibitors.

Patients must have had an inadequate response, loss of response, or intolerance to prior immunosuppressant and/or corticosteroid treatment.

Patients who are on background immunosuppressant therapy (6-MP, AZA, MTX) may be enrolled if they have received a stable dose for at least 8 weeks prior to randomization (Day 1). Such patients should continue on their stable baseline doses of their background immunosuppressant therapy throughout the study unless dose reduction or discontinuation is required due to toxicity. 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 remains at the discretion of the investigator.

Patients on oral corticosteroid therapy (prednisone at a stable dose of ≤30 mg, or equivalent) may be enrolled according to the following criteria:

- If corticosteroid therapy is ongoing or has just been initiated, the dose has to be stable for at least 4 weeks immediately prior to randomization (Day 1)
- If corticosteroids are being tapered, the dose has to be stable for 2 weeks immediately prior to randomization (Day 1)

Such patients should continue stable doses of their background corticosteroid until Week 10, at which point a corticosteroid taper will be initiated for all patients entering the Maintenance Phase.

Initiation of corticosteroid or an increase in corticosteroid dose above the patients' entry dose (up to a maximum of 30 mg/day of prednisone [or equivalent]) will not be permitted during screening. Use of budesonide will be allowed at stable doses (≤9 mg) provided that the dose has been stable for ≥4 weeks prior to randomization (Day 1). Oral 5-ASA

treatment and probiotics for the treatment of UC may be continued at a stable dose as long as the dose(s) had been stable for ≥4 weeks and ≥2 weeks, respectively, prior to randomization (Day 1). Certain concomitant treatments are prohibited (see Section 4.5.2 for list of all prohibited concomitant treatments).

Patients must have discontinued topical treatments for UC at least 2 weeks prior to randomization (Day 1).

The study will be divided into:

- Screening period of up to 35 days (for details see Section 4.7.2.1)
- Double-blind treatment period of 54 weeks, composed of an Induction Phase (up to Week 10) and a Maintenance Phase (Week 10 to Week 54)
- Safety follow-up period of 12 weeks

A total of approximately 390 patients will be recruited (see Figure 1) from approximately 200 sites. Patients will be stratified by concomitant treatment with corticosteroids (including budesonide) at baseline (yes/no), concomitant treatment with immunosuppressants at baseline (yes/no), and baseline disease activity as measured during screening (MCS ≤9 vs. MCS ≥10).

Patients completing the Maintenance Phase at Week 54, patients identified as having disease worsening between Weeks 10 and 54 (Section 3.1.1.1), or patients who receive defined rescue medication(s) (Section 3.1.1.2) may enroll in Part 1 (OLE) of Study GA28951, if eligible, where they will receive open-label etrolizumab after a brief washout phase. If they do not enroll in Part 1 (OLE) of Study GA28951, they will enter the 12-week safety follow-up period of this study and will then be requested to enroll in Part 2 (SM) of Study GA28951 for 92 weeks of extended PML monitoring.

Study Drug Administration

Following screening, patients will be randomized in a 1:1 ratio to receive 105 mg etrolizumab or 5 mg/kg infliximab. The study design is double-blind, double-dummy, so all patients will receive two study treatments, either active etrolizumab + infliximab dummy, or active infliximab + etrolizumab dummy. The dummy for etrolizumab will be a matched SC placebo, whereas the dummy for infliximab will be an IV saline infusion. Patients will receive either 105 mg etrolizumab or etrolizumab dummy by SC administration Q4W until Week 52. Infliximab will be administered by IV infusion at Weeks 0, 2, and 6 and then every 8 weeks (Q8W) until Week 46. Consequently, administration of SC study medication and IV study medication occurs at different timepoints throughout the study.

The first 2 doses of etrolizumab/etrolizumab dummy will be administered via a prefilled syringe (PFS) by a health care professional (HCP) in the clinic. The subsequent two doses will be self-administered by the patient or administered by his or her caregiver in the clinic and monitored by the HCP.

If deemed appropriate by HCP, the remaining doses of etrolizumab/etrolizumab dummy study drug, starting at Week 16, will be self-administered by the patient or administered by his or her caregiver at home Q4W (action to be taken as a result of a hypersensitivity reaction provided in Section 5.1.1.2). On occasions when the patient has to attend the clinic the same day as an etrolizumab/etrolizumab dummy administration, the administration of study medication by the patient or his or her caregiver will occur at home after his or her study assessments in the clinic setting. If necessary, patients or their HCPs may choose to continue administration of study medication in the clinic. The details of study medication administration are provided in Section 4.4.2.

In addition, patients will receive either infliximab (5 mg/kg IV at Weeks 0, 2, and 6, then Q8W) or infliximab dummy (saline) IV at the same timepoints, administered in the clinic setting until Week 46.

Oral Corticosteroids during the Study

During the Induction Phase, patients are to maintain their stable, baseline corticosteroid dose. Corticosteroids are to be tapered starting from Week 10 for all patients entering the Maintenance Phase. Patients receiving prednisone at a dose of >10 mg/day (or equivalent) are to have their dose reduced at a rate of 5 mg per week until a 10 mg/day dose is achieved. Patients receiving prednisone at doses ≤ 10 mg/day (or equivalent), or once a 10 mg/day dose (or equivalent) is achieved by tapering, are to have their dose reduced at a rate of 2.5 mg/week until discontinuation. Beginning at Week 10, patients receiving budesonide should taper their dose of 9 mg every day to 9 mg every other day for 2 weeks and then discontinue budesonide treatment. For patients who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms of either UC or steroid withdrawal, corticosteroid dose may be increased (up to the dose at study entry if required), but tapering must begin again within 2 weeks.

Investigators are to inform their patients to contact them if they are experiencing disease symptoms or steroid withdrawal symptoms during the taper.

Immunosuppressants during the Study

Patients should remain on their stable baseline doses of immunosuppressants (AZA, 6-MP, MTX) throughout the study unless dose reduction or discontinuation is required because of a toxicity related to the medication. 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 remains at the discretion of the investigator.

3.1.1.1 Disease Worsening

Disease worsening is defined as:

An increase in the partial Mayo Clinic Score (pMCS) ≥ 3 points from Week 10

AND an absolute pMCS ≥ 5

AND an endoscopy subscore of ≥ 2

OR

An absolute pMCS score ≥ 7

AND an endoscopy subscore of ≥ 2

If a patient meets criteria for disease worsening during the Maintenance Phase of the study (Week 10 to Week 54), he or she may withdraw from this study and enroll, if eligible, in Part 1 (OLE) of Study GA28951 to receive open-label etrolizumab after completing a brief washout phase.

3.1.1.2 Rescue Therapy

Rescue Therapy That Can Be Given with Study Medication for the Treatment of Ulcerative Colitis

<u>During the Induction Phase (Prior to Week 10)</u>

Patients should maintain stable doses of their concomitant medications (e.g., oral 5-ASA, corticosteroids, immunosuppressants) for UC.

During the Induction Phase, any patient who requires initiation of an immunosuppressant (AZA, 6 MP, or MTX), corticosteroid, or oral or topical 5-ASA, or who requires an increase in dose over baseline levels for treatment of worsening disease symptoms, should stay in the study. These patients will be considered non-responders for the Induction timepoint.

<u>During the Maintenance Phase (Week 10 to Week 54)</u>

Initiation or escalation of oral 5-ASA should be avoided but is permitted if deemed clinically necessary by the investigator. Patients who initiate or escalate oral 5-ASA therapy may continue blinded treatment.

Corticosteroids: Use of topical or IV corticosteroids, or topical 5-ASA is not desired as concomitant medication. If these are used to treat clinical symptoms of UC, the patient may remain in the blinded study or may enter, if eligible, Part 1 (OLE) of Study GA28951 after a brief washout phase and based on the investigator's discretion.

Patients on corticosteroids at baseline must begin the specified corticosteroid taper at Week 10. For patients who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms of either UC or steroid withdrawal, corticosteroids may be increased

(up to the baseline dose, only if required). In such cases, the tapering regimen must be reinitiated within 2 weeks. An increase in corticosteroid dose back to baseline is not considered rescue medication if it occurs during the corticosteroid taper. These patients should remain in the study.

Patients who were not receiving corticosteroids at baseline and patients who have completed the steroid taper who subsequently require oral corticosteroids at a dose greater than 10 mg for 5 days or longer for the treatment of worsening UC symptoms or steroid withdrawal may remain in the study or may enroll, if eligible, in Part 1 (OLE) of Study GA28951 after a brief washout phase and based on the investigator's discretion.

Immunosuppressants (AZA, 6-MP, or MTX): Patients are to remain on their stable baseline dose of immunosuppressant therapy throughout the study unless dose reduction or discontinuation is required due to toxicity. 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 remains at the discretion of the investigator. Patients who do initiate or escalate immunosuppressant therapy may remain in the study or may be given the option to enter Part 1 (OLE) of Study GA28951, if eligible, after a brief washout phase and based on the investigator's discretion.

Endoscopy to document disease activity for patients exiting the treatment period early for any reason *may be performed at the discretion of the investigator.*

Prohibited Rescue Therapy

At ANY time during the conduct of the study, use of other immunosuppressive agents including, but not limited to, anti-integrins, T- or B-cell depleters (except agents such as AZA and 6-MP), TNF inhibitors (including TNF inhibitor biosimilars), anti-adhesion molecules, *Janus kinase (JAK) inhibitors,* cyclosporine, tacrolimus, or investigational agents are prohibited. Use of anakinra, abatacept, tocilizumab, and other biological therapeutics are also prohibited.

Patients who receive such therapies are not to receive further study treatment or open-label treatment, and will be required to enter the 12-week safety follow-up period of this study (see Appendix 2). These patients will also be requested to enroll in Part 2 (SM) of Study GA28951 for 92 weeks of extended PML monitoring.

3.1.1.3 Infliximab Washout Period

Infliximab Washout Period for Patients Who Will Receive Open-Label Etrolizumab Treatment in Study GA28951

Prior to switching to Part 1 (OLE) of Study 28951, eligible patients (see Section 4.7.2.3.1 for eligibility criteria for switch to open-label treatment) are to undergo a blinded washout period of 6 or 8 weeks (see Table 3) measured since the last infusion of infliximab/infliximab dummy. This is required to ensure adequate washout of infliximab in those patients randomized to active infliximab.

During this washout, all patients will remain on blinded SC study medication (etrolizumab/etrolizumab dummy) and blinded IV study medication (infliximab/infliximab dummy) will cease. Consequently, patients randomized to active etrolizumab will continue to receive etrolizumab and patients randomized to active infliximab will continue to receive etrolizumab dummy during the blinded washout period. This mandated washout phase will lead to delayed entry into Part 1 (OLE) of Study GA28951 by 0 to 5 weeks (see Table 3 for schedule).

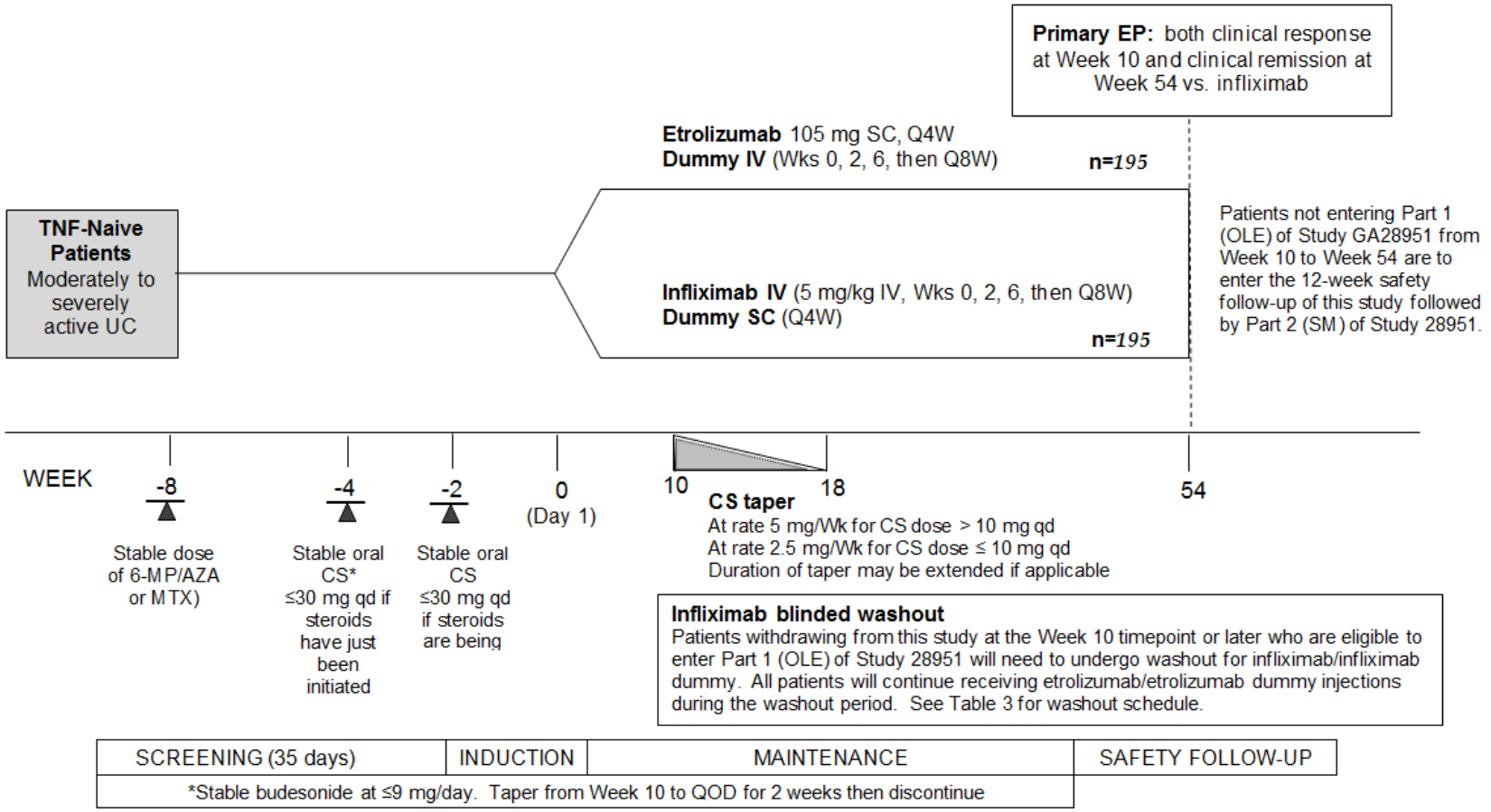
The evaluation of eligibility for Part 1 (OLE) of Study GA28951 can be made at study visits, telephone contacts, and/or unscheduled visits. If eligible, the decision to switch to (but not necessarily enter) Part 1 (OLE) of Study GA28951 can occur at the visits listed in Table 3, with the earliest timepoint being the Week 10 visit, and occurring every week up to Week 52. The assessments listed for "Unscheduled Visit/Decision to Switch to OLE" should be followed (see Appendix 1). The earliest timepoint for entry into Part 1 (OLE) of Study GA28951 is at the Week 12 visit and the latest is at the Week 54 visit. Due to the washout period, entry into Part 1 (OLE) of Study GA28951 may be delayed by up to 5 weeks from the visit date at which the decision to switch is made and detailed scenarios are outlined in Table 3.

During the blinded washout period, rescue therapy with corticosteroids (IV, oral, or topical) and/or immunosuppressants (AZA, 6-MP, or MTX) for worsening UC is permitted at the discretion of the investigator. Addition of or increases in doses of 5-ASA (oral or topical) will also be permitted per the investigator's discretion.

At the end of the washout period, patients are to have early withdrawal/end of washout assessments AND NOT their scheduled clinic visit/telephone contact assessments prior to enrollment into (Part 1) (see Appendix 1).

A complete list of study visits and assessments can be found in the Schedule of Assessments (see Appendix 1). A complete list of eligibility for enrollment of patients into Part 1 (OLE) of Study GA28951 can be found in Table 5.

Figure 1 Study Schema



6-MP = 6-mercaptoprine; AZA = azathioprine; CS = corticosteroid; EP = endpoint; IV = intravenous; MTX = methotrexate; OLE = open-label extension; SM = safety-monitoring; Q4W = every 4 weeks; Q8W = every 8 weeks; qd = once a day; QOD = every other day; SC = subcutaneous; SM = safety monitoring; TNF-naive = naive to tumor necrosis factor inhibitor; Wk = week.

3.1.1.4 Number of Patients

A total of approximately *390* patients will be enrolled in this study from approximately 200 sites. Patients will be randomized into one of two study groups in a 1:1 ratio as follows:

- Group A: 105 mg etrolizumab SC Q4W until Week 52 plus infliximab dummy IV at Weeks 0, 2, and 6 and Q8W thereafter until Week 46.
- Group B: 5 mg/kg infliximab IV at Weeks 0, 2, and 6 and Q8W thereafter until Week 46 plus etrolizumab dummy SC Q4W until Week 52.

3.1.2 Data Monitoring Committee

An independent data monitoring committee (iDMC) will monitor safety and study conduct on an ongoing basis. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines the iDMC roles and responsibilities. The iDMC will meet approximately every 6 months (frequency adjustable as required) to review unblinded safety and study conduct data prepared by an independent data coordinating center (IDCC). If the iDMC deems a benefit–risk assessment necessary, the iDMC may also review unblinded efficacy data. The iDMC may recommend stopping the study early for safety reasons. However, the iDMC may not recommend stopping the study early for positive efficacy or solely for futility.

3.2 END OF STUDY AND LENGTH OF STUDY

Length of Study

The total length of the treatment period will be 54 weeks. Patients who have disease worsening between Weeks 10 and 54, patients who receive defined rescue treatment(s) (see Section 4.4.2.3), and patients who complete 54 weeks of the study may be given the option of enrolling in Part 1 (OLE) of Study GA28951, where they will receive open-label etrolizumab treatment.

Those who do not enroll in Part 1 (OLE) of Study GA28951 will continue to 12 weeks of safety follow-up in this protocol (without the washout phase) and then be requested to enroll in Part 2 (SM) of Study GA28951 for 92 weeks of PML monitoring.

The total length of the study is expected to last from the first patient screened to either the last patient in last safety follow-up visit in this protocol or the last patient enrolled into Study GA28951, whichever is later.

End of Study

The end of the study is defined as the last patient last safety follow-up visit in this protocol, or last patient in this protocol enrolled in Study GA28951, whichever is later.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Test Product Dosage

Data from Phase I (Study ABS4262g) and Phase II (Study ABS4986g; EUCALYPTUS) indicated that the nominal 100-mg Q4W regimen is sufficient to maintain β7 receptor occupancy both in blood and in colonic tissue, is well tolerated, and results in meaningful clinical efficacy, and therefore, will be evaluated further in this Phase III study. The rationale for proposing a 105-mg Q4W SC regimen is discussed below.

- In the Phase II, the nominal 100-mg Q4W SC dose (0.7 mL of 150 mg/mL solution via vial and syringe, with an actual dose of 105 mg) showed clinically meaningful efficacy without clinically meaningful safety imbalances (see Section 1.2). The Phase III formulation is a PFS containing 0.7 mL of 150 mg/mL etrolizumab solution, corresponding to delivering a dose of 105 mg etrolizumab per injection.

  In the Phase II EUCALYPTUS study, the 100-mg SC Q4W dose resulted in an increased clinical remission rate in TNF-naive patients (43.8%; $p = 0.007$), as well as in the combined TNF-naive and inadequate response to anti-tumor necrosis factor (TNF-IR) group (20.5%; $p = 0.004$) at Week 10 as compared with the clinical remission rate in placebo patients (0%). These data suggest that the 100-mg SC Q4W dose regimen is efficacious in patients with moderately and severely active UC.

- Up to a 4–5-fold higher exposure did not result in a greater PD effect or an increase in clinical benefit.

  A higher dose (420 mg SC at Week 0 followed by 300 mg at Weeks 2, 4, and 8) was also tested in the EUCALYPTUS study without any major safety concerns. However, there was no clear distinction in observed pharmacological effects (including clinical efficacy outcome and PD response, such as β7 receptor occupancy) between high-dose and the 100-mg dose cohorts. Although the study was not powered to enable a formal comparison of the two active arms, the data suggest that the observed clinical remission rate at Week 10 in the low-dose cohort was not further improved in the high-dose cohort.

  Preliminary concentration quartile-response analysis was conducted, for the data pooled from both low- and high-dose cohorts, to see whether patients in the higher concentration quartiles had better remission rate. The results did not show any exposure response relationship.

- Exposure lower than 100 mg Q4W is likely not sufficient to maintain β7 integrin receptor occupancy.

  In the Phase I study (Study ABS4262g), the etrolizumab PK profile appears nonlinear at a dose level of < 1 mg/kg IV. The duration of β7 receptor occupancy is dose dependent. A single dose of 0.3 mg/kg IV maintained β7 receptor occupancy for only approximately 2 weeks, which is likely insufficient to ensure maximal β7 receptor occupancy at all times within a Q4W dosing interval.

On the basis of data from the Phase II EUCALYPTUS study, it is assumed that maximal/near maximal occupancy of β7 receptors both in the blood and in colonic tissue is minimally necessary for etrolizumab's clinical activity. Per this assumption, population PK simulations were performed and results showed that a 100-mg SC Q4W regimen can provide steady-state serum trough concentration ($C_{trough,ss}$) of at least 1.7 μg/mL (the minimum serum concentration observed that maintained colonic tissue β7 occupancy) in ≥84% of patients, whereas a dose lower than the 100-mg SC Q4W regimen (e.g., 50 mg Q4W SC) is likely not sufficient for maintaining β7 receptor occupancy at all times during the Q4W dosing interval, since only 56% of patients were predicted to reach a 1.7 μg/mL level in their $C_{trough,ss}$ (see Table 2).

Lower doses are also anticipated to result in etrolizumab serum level falling into the nonlinear PK concentration range and hence are likely to increase variability in exposure.

Table 2 Population Pharmacokinetic Modeling Predicted Percentage of Patients Achieving 1.7-μg/mL Steady-State Trough Concentration under Different Dosing Scenarios

	Q4W SC Dosing		
	300 mg	100 mg	50 mg
Percentage of patients expected to have $C_{trough,ss}$ > 1.7μg/mL	98	84	56

$C_{trough,ss}$ = steady-state trough concentrations; Q4W = every 4 weeks; SC = subcutaneous.

Note: 1.7 μg/mL is the minimum serum concentration observed in the Phase II study that maintained β7 occupancy in the colonic tissue.

In conclusion, on the basis of available etrolizumab efficacy, PK, PD, and safety data (see Section 1.2), a PFS delivering a dose of 105 mg Q4W is considered the most appropriate dosing regimen for this Phase III study.

3.3.2 Rationale for Patient Population

There is a high unmet medical need in moderately to severely active UC due to current treatments being associated with significant adverse events, resulting in low rates of sustained remission, or being highly invasive (i.e., colectomy) (see Section 1.1 for details).

The Phase II EUCALYPTUS study provided evidence of efficacy, including induction of remission at Week 10, in patients with moderately to severely active UC refractory to or intolerant of conventional and/or TNF inhibitor therapies. Results from this study showed that at Week 10, the proportions of patients in clinical remission (defined as MCS ≤2 and all subscores ≤1) in the overall population were 20.5% in the 100-mg arms, compared with 0% in the placebo arm. In the TNF-naive subgroup, clinical remission at

Week 10 was observed in 43.8% versus 0% of patients in the 100 mg etrolizumab versus placebo group suggesting substantial efficacy in the TNF-naive population at Week 10.

In summary, because of the limitations of the currently available therapies for the treatment of moderately to severely active UC, the decrease in clinical remission seen over time with TNF inhibitors, and the favorable benefit-risk observed in the TNF-naive population in EUCALYPTUS, this Phase III study is designed to test the efficacy and safety of etrolizumab in this patient population compared with the current standard-of-care (SOC) medication infliximab.

3.3.3 Rationale for Active Comparator

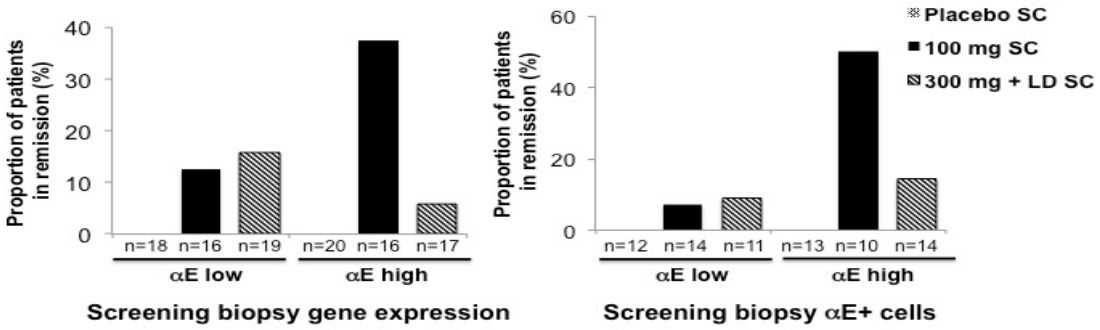
Although at present, TNF inhibitors appear to be the most effective biologic therapy in moderately to severely active UC, no currently available therapy achieves sustained remission in more than 10%–30% of patients with IBD who have chronic disease (Hanauer et al. 2002; Sandborn et al. 2005). Furthermore, adverse events associated with TNF inhibitors include elevated rates of serious bacterial infection, including TB, and (more rarely) lymphoma and demyelination (Chang and Lichtenstein 2006).

This study is designed to compare the efficacy and safety of etrolizumab with that of an active comparator, infliximab (TNF inhibitor), which is an SOC biologic for the treatment of moderately to severely active UC.

3.3.4 Rationale for Biomarker Assessments

A biomarker that may predict an increased chance of response to therapy would be valuable to patients and treating physicians to aid in guiding treatment decisions. Etrolizumab binds to the $\beta7$ integrin and blocks $\alpha4\beta7$:MAdCAM and $\alpha E\beta7$:E-cadherin binding. In exploratory analyses from the Phase II EUCALYPTUS study, patients with higher baseline biopsy αE gene expression by quantitative polymerase chain reaction (qPCR) and αE^+ cell counts by immunohistochemistry (IHC) had a higher rate of remission at Week 10 (see Figure 2). The baseline levels of αE and other biomarkers will be evaluated in the Phase III study to further evaluate whether they may function as predictive response biomarkers in the TNF-naive patient population.

Figure 2 Effects of High and Low Baseline Expression of the αE Biomarker in Colon on the Remission Status of TNF-Naive Ulcerative Colitis Patients Treated with Etrolizumab



LD = loading dose; SC = subcutaneous.

All patients enrolled in the current study will have mandatory colonic mucosal sampling at the baseline visit to analyze the relationship of αE levels (and possibly other biomarkers) with response to treatment. In addition, *biomarker* samples *from blood and tissue* will be collected at Weeks 10 and 54 for potential exploratory PD biomarker analyses.

Additional biomarkers, including, but not limited to, protein biomarkers or mRNA gene expression will be assessed at baseline and after treatment to increase the knowledge and understanding of disease biology, patient populations, etrolizumab mechanism of action and relationships to exposure, and inform biomarkers predictive of response to treatment.

In addition, stool samples will be collected at Week 10 and Week 54 for assessment of stool biomarkers including, but not limited to, microbiome or products of bacterial cultures.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

Primary Efficacy Outcome Measure

- Both clinical response at Week 10 and clinical remission at Week 54 in patients with UC as determined by the MCS

Secondary Efficacy Outcome Measures

- Clinical remission at Week 10
- Clinical remission at Week 54

- Clinical remission achieved at both Week 10 and Week 54
- *Clinical remission at Week 54 among patients with a clinical response at Week 10*
- Improvement in endoscopic appearance of the mucosa at Week 10
- Improvement in endoscopic appearance of the mucosa at Week 54
- Improvement in endoscopic appearance of the mucosa achieved at both Week 10 and Week 54
- Endoscopic remission at Week 54
- Clinical response at Week 10
- Clinical response achieved at both Week 10 and Week 54
- Corticosteroid-free clinical remission at Week 54 (off corticosteroids for at least 24 weeks prior to Week 54) in patients who were receiving corticosteroids at baseline
- Change from baseline in patient-reported health-related QOL at Weeks 10, 30, and 54, as assessed by the Inflammatory Bowel Disease Questionnaire (IBDQ)

Exploratory Efficacy Outcome Measures

- Remission at Week 10
- Remission at Week 54
- Remission at both Week 10 and Week 54
- Change in health utilities, as assessed by the EuroQoL Five-Dimension Questionnaire (EQ-5D), from baseline to Weeks 10, 30, and 54
- Frequency and duration of hospitalizations from baseline to Week 54

3.4.2 Safety Outcome Measures

The safety outcome measures for 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 study drug discontinuation
- Incidence of laboratory abnormalities
- Incidence of malignancies
- Incidence of ATAs to etrolizumab, or if necessary, infliximab
- Incidence and severity of hypersensitivity reaction events

3.4.3 Pharmacokinetic Outcome Measures

The etrolizumab PK assessment will be performed in a subset of etrolizumab-treated patients. The PK outcome measures for this study are as follows:

- Serum concentration 2 weeks after the first dose and at steady state during the dosing period from Week 12 to Week 54
- Serum concentration at timepoints Weeks 10, 30, and 54

3.4.4 Exploratory Biomarker Outcome Measures

The exploratory biomarker outcome measures for this study are as follows:

- Relationship between remission and baseline levels of colonic tissue biomarkers and/or peripheral blood including, but not limited to, αE integrin. *These may be outcomes predictive or prognostic of response.*
- Changes in stool biomarkers, which may include, but are not limited to, those in the microbiota and bacterial cultures, during the Induction and Maintenance Phases as compared to baseline

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population is TNF-naive patients with moderately to severely active UC (defined as MCS of 6–12, endoscopy subscore of ≥2 as determined by the central reading procedure described in Section 4.7.1.4, a rectal bleeding subscore ≥1, a stool frequency subscore ≥1, and colonic involvement extending a minimum of 20 cm from the anal verge).

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Able and willing to provide written informed consent
- 18–80 years of age, inclusive
- Diagnosis of UC established at least 3 months prior to randomization (Day 1) by clinical and endoscopic evidence. This diagnosis should be corroborated by histopathology conducted at any time prior to screening and documented by a histopathology report. (Note: histopathology may be performed at screening, if no prior report is readily available.)
- Moderately to severely active UC as determined by an MCS of 6–12, with an endoscopic subscore ≥2 as determined by the central reading procedure described in Section 4.7.1.4, a rectal bleeding subscore ≥1, and a stool frequency subscore ≥1 during the screening period (prior to randomization [Day 1]). See also Section 4.7.2.1 for additional information regarding this time window.

- Evidence of UC extending a minimum of 20 cm from the anal verge as determined by baseline endoscopy (flexible sigmoidoscopy or colonoscopy) performed during screening, 4–16 days prior to randomization (Day 1). See also Section 4.7.2.1 for additional information regarding this time window.
- Naive to treatment with any TNF inhibitor therapy (including TNF inhibitor biosimilars)
- Patients must have had an inadequate response, loss of response, or intolerance to prior immunosuppressant and/or corticosteroid treatment.

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

  Persistent signs and symptoms of active disease despite a history of at least one 12-week regimen of oral AZA (≥ 1.5 mg/kg) or 6-mercaptopurin (6–MP; ≥ 0.75 mg/kg) and/or MTX (≥ 15 mg/week) within the previous 5 years

  Persistent signs and symptoms of active disease despite a 6-TG level of ≥ 230 pmol/8 × 108 RBCs during at least one 12-week regimen of oral AZA or 6-MP at a stable or increasing dose within the previous 5 years

  History of intolerance to AZA, 6-MP, or MTX (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, LFT abnormalities, lymphopenia, TPMT genetic mutation, infection) within the previous 5 years

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

  Steroid refractory: persistent symptoms of active disease despite treatment with at least one 4-week induction regimen that included a dose of ≥ 30 mg prednisone (oral) daily (or equivalent) for at least 2 weeks or IV for at least 1 week within the previous 5 years

  Steroid dependent: two failed attempts to taper steroids below a dose equivalent to 10 mg prednisone (oral) daily

  Steroid intolerant: history of intolerance to corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection) within the previous 5 years
- Any ongoing UC therapy must be at stable doses:

  May be receiving oral 5-ASA compounds provided that the dose has been stable for ≥ 4 weeks immediately prior to randomization (Day 1)

  May be receiving oral corticosteroid therapy (prednisone at a stable dose of ≤ 30 mg a day, or equivalent steroid)

  If corticosteroid therapy is ongoing or has recently been initiated, the dose has to be stable for at least 4 weeks immediately prior to randomization (Day 1). If corticosteroids are being tapered, the dose has to be stable for at least 2 weeks immediately prior to randomization.

  May be receiving budesonide therapy at a stable dose of up to 9 mg a day for ≥ 4 weeks prior to randomization (Day 1)

May be receiving probiotics (e.g., Culturelle, *Saccharomyces boulardii*), provided that the dose has been stable for ≥2 weeks immediately prior to randomization (Day 1)

May be receiving AZA, 6-MP, or MTX, provided that the dose has been stable for ≥8 weeks immediately prior to randomization (Day 1)

- For women who are not postmenopausal (at least 12 months of non–therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or 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 3).

  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.

- Must have received a colonoscopy within the past year or be willing to undergo a colonoscopy in lieu of a flexible sigmoidoscopy at screening. This colonoscopy must:

  Confirm disease extent (defined as 1) left-sided colitis [up to the splenic flexure], 2) extensive colitis [beyond the splenic flexure but not involving the entire colon], and 3) pancolitis; see Section 4.7.1.4)

  Include removal of any adenomatous polyps

  Document evidence of surveillance for dysplasia for all patients with left-sided colitis of >12 years' duration and total/extensive colitis of >8 years' duration

4.1.2 Exclusion Criteria

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

Exclusion Criteria Related to Inflammatory Bowel Disease

- Prior extensive colonic resection, subtotal or total colectomy, or planned surgery for UC
- Past or present ileostomy or colostomy
- Diagnosis of indeterminate colitis
- Suspicion of ischemic colitis, radiation colitis, or microscopic colitis
- Diagnosis of toxic megacolon within 12 months of initial screening visit
- Any diagnosis of Crohn's disease
- Past or present fistula or abdominal abscess
- A history or current evidence of colonic mucosal dysplasia
- Patients with any stricture (stenosis) of the colon
- Patients with history or evidence of adenomatous colonic polyps that have not been removed

Exclusion Criteria Related to Prior or Concomitant Therapy

- Any prior treatment with etrolizumab or other anti-integrin agents (including natalizumab, vedolizumab, and efalizumab)
- Any prior treatment with anti-adhesion molecules (e.g., anti-MAdCAM-1)
- Any prior treatment with rituximab
- *Any treatment with tofacitinib during screening*
- Use of IV steroids within 30 days prior to screening with the exception of a single administration of IV steroid
- Use of agents that deplete B or T cells (e.g., alemtuzumab or visilizumab) within 12 months prior to randomization (Day 1), with the exception of AZA and 6-MP
- Use of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) within 4 weeks prior to randomization (Day 1)
- Chronic nonsteroidal anti-inflammatory drug (NSAID) use (Note that occasional use of NSAIDs and acetaminophen [e.g., headache, arthritis, myalgias, or menstrual cramps] and aspirin up to 325 mg daily is permitted.)
- Patients who are currently using anticoagulants including, but not limited to, warfarin, heparin, enoxaparin, dabigatran, apixaban, rivaroxaban. (Note that antiplatelet agents such as aspirin up to 325 mg daily or clopidogrel are permitted.)
- Patients who have received treatment with corticosteroid enemas/suppositories and/or topical (rectal) 5-ASA preparations within 2 weeks prior to randomization (Day 1)
- Apheresis (i.e., Adacolumn apheresis) within 2 weeks prior to randomization (Day 1)

- Received any investigational treatment including investigational vaccines within 5 half-lives of the investigational product or 28 days after the last dose (whichever is greater) prior to randomization (Day 1) of the study
- History of moderate or severe allergic or anaphylactic/anaphylactoid reactions to chimeric, human, or humanized antibodies, fusion proteins, or murine proteins or hypersensitivity to etrolizumab (active drug substance) or any of the excipients (L-histidine, L-arginine, succinic acid, polysorbate 20)
- Patients administered tube feeding, defined formula diets, or parenteral alimentation/nutrition who have not discontinued these treatments ≥ 3 weeks prior to randomization (Day 1)

Exclusion Criteria Related to General Safety

- Pregnant or lactating
- Lack of peripheral venous access
- Hospitalized (other than for elective reasons) during the screening period
- Inability to comply with study protocol, in the opinion of the investigator
- Significant uncontrolled comorbidity, such as cardiac (e.g., moderate to severe heart failure New York Heart Association [NYHA] Class III/IV), pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders (excluding UC)
- Neurologic conditions or diseases that may interfere with monitoring for PML
- History of demyelinating disease
- Clinically significant abnormalities on screening neurologic examination (PML Objective Checklist)
- Clinically significant abnormalities on the screening PML Subjective Checklist
- History of alcohol, drug, or chemical abuse ≤ 6 months prior to screening
- Conditions other than UC that could require treatment with > 10 mg/day of prednisone (or equivalent) during the course of the study
- History of cancer, including hematologic malignancy, solid tumors, and carcinoma in situ, within 5 years before screening with the following exceptions:

  Local basal or squamous cell carcinoma of the skin that has been excised and is considered cured is not exclusionary.

  A history of chronic myelogenous leukemia, hairy cell leukemia, melanoma, renal cell carcinoma, or Kaposi sarcoma is exclusionary irrespective of the duration of time before screening.

  History of a cervical smear indicating the presence of adenocarcinoma in situ (AIS), high-grade squamous intraepithelial lesions (HSIL), or cervical intraepithelial neoplasia (CIN) of Grade > 1, is exclusionary, irrespective of the duration of time before screening.

Exclusion Criteria Related to Infection Risk

- Congenital or acquired immune deficiency
- Patients must undergo screening for HIV and test positive for preliminary and confirmatory tests
- Positive hepatitis C virus (HCV) antibody test result, unless the patient (1) has undetectable HCV RNA levels for $>$6 months after completing a successful course of HCV anti-viral treatment and an undetectable HCV RNA at screening or (2) has a known history of HCV antibody positivity with a history of undetectable HCV RNA for $>$6 months and undetectable HCV RNA at screening in the absence of history of HCV anti-viral treatment.
- Patients must undergo screening for hepatitis B virus (HBV). This includes testing for HBsAg (HBV surface antigen), anti-HBc total (HBV core antibody total), and HBV DNA (patients who test negative for these tests are eligible for this study):

  Patients who test positive for surface antigen (HBsAg+) are not eligible for this study, regardless of the results of other hepatitis B tests.

  Patients who test positive only for core antibody (anti-HBc+) must undergo further testing for hepatitis B DNA (HBV DNA test).

    If the HBV DNA test result is positive, the patient is not eligible for this study.

    In the event the HBV DNA test cannot be performed, the patient is not eligible for this study.

    If the HBV DNA test is negative, the patient is eligible for this study. These patients will undergo periodic monitoring for HBV DNA during the study.
- Evidence of or treatment for *Clostridium difficile* (as assessed by C. difficile toxin testing) within 60 days prior to randomization (Day 1) or other intestinal pathogens (as assessed by stool culture and ova and parasite evaluation) within 30 days prior to randomization (Day 1)
- Evidence of or treatment for clinically significant cytomegalovirus (CMV) colitis (based on the investigator's judgment) within 60 days prior to randomization (Day 1). Laboratory confirmation of CMV from a colon biopsy sample is required during screening evaluation only if clinical suspicion is high and to determine the need for CMV treatment
- History of active or latent TB regardless of treatment history (see Section 4.7.1.5)

    Patients with a history of active or latent TB (based on a positive screening assay, either purified protein derivative [PPD] skin test or QuantiFERON®TB Gold test, see Section 4.7.1.5) are not eligible for this study.

    Patients with a chest X-ray (posteroanterior [PA] and lateral) within 3 months of enrollment suspicious for pulmonary TB are **not** eligible for this study.

    Any immunosuppressed patient with a strong suspicion of TB exposure and no prior vaccination with bacille Calmette-Guérin (BCG) should be considered at risk for having latent TB infection.

Patients at risk for TB exposure include:

Patients who have household contact with a person with active TB

Patients living in areas with high incidence of TB

Patients who frequently visit areas with high prevalence of active TB

Patients who meet these criteria should be evaluated per local practice to exclude latent TB.

- History of recurrent opportunistic infections and/or history of severe disseminated viral infections (e.g., herpes)
- Any serious opportunistic infection within the last 6 months
- Any current or recent signs or symptoms (within 4 weeks before screening and during screening) of infection, except for the following:

  Minor infections (e.g., common cold) that have, in the investigator's judgment, completely resolved prior to randomization (Day 1)

  Fungal infections of the nail beds

  Oral or vaginal candidiasis that has resolved with or without treatment prior to randomization (Day 1)
- Any major episode of infection requiring treatment with IV antibiotics within 8 weeks prior to screening or oral antibiotics within 4 weeks prior to screening

  Treatment with antibiotics as adjunctive therapy for UC in the absence of documented infection is not exclusionary.
- Received a live attenuated vaccine within 4 weeks prior to randomization (Day 1)
- History of organ transplant

Exclusion Criteria Related to Laboratory Values (at Screening)

- Serum creatinine $> 2 \times$ upper limit of normal (ULN)
- ALT or AST $> 3 \times$ ULN or alkaline phosphatase $> 3 \times$ ULN or total bilirubin $> 2.5 \times$ ULN (unconjugated hyperbilirubinemia that is associated with known Gilbert's syndrome is not an exclusion criterion)
- Platelet count $< 100{,}000/\mu L$
- Hemoglobin < 8 g/dL
- Absolute neutrophil count $< 1500/\mu L$
- Absolute lymphocyte count $< 500/\mu L$

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Patients will be randomized to the two treatment arms through an interactive voice/Web-based response system (IxRS). After written informed consent has been obtained, all patients will receive a screening number that will be assigned by the IxRS. Following completion of up to a 35-day screening period and after all patient eligibility requirements are confirmed, patients will be assigned a subject number (a different

number from the screening number) on Day 1 and will be randomized in a 1:1 ratio to one of two treatment arms (105 mg etrolizumab SC or 5 mg/kg infliximab IV) for the 54-week double-blind period (see Figure 3 for details of study drug administration schedule).

Patients will be randomized on the same day that treatment is to be initiated (Day 1). Randomization will be stratified by concomitant treatment with corticosteroids including budesonide at baseline (yes/no), concomitant treatment with immunosuppressants at baseline (yes/no), and baseline disease activity as measured during screening (MCS $\leq$ 9/MCS $\geq$ 10). A permuted blocks randomization method will be used to obtain approximately a 1:1 ratio between the two treatment arms and within each stratum.

During the 54-week double-blind treatment period and the infliximab washout period, the IxRS will make etrolizumab/etrolizumab dummy kit assignments. Each kit will consist of one prefilled 1-mL syringe (0.7 mL nominal volume). Study drug kits will be assigned for administration to each patient; the number of kits assigned will allow for administration up until the next clinic visit. The placebo and active kits are filled and packaged to look identical.

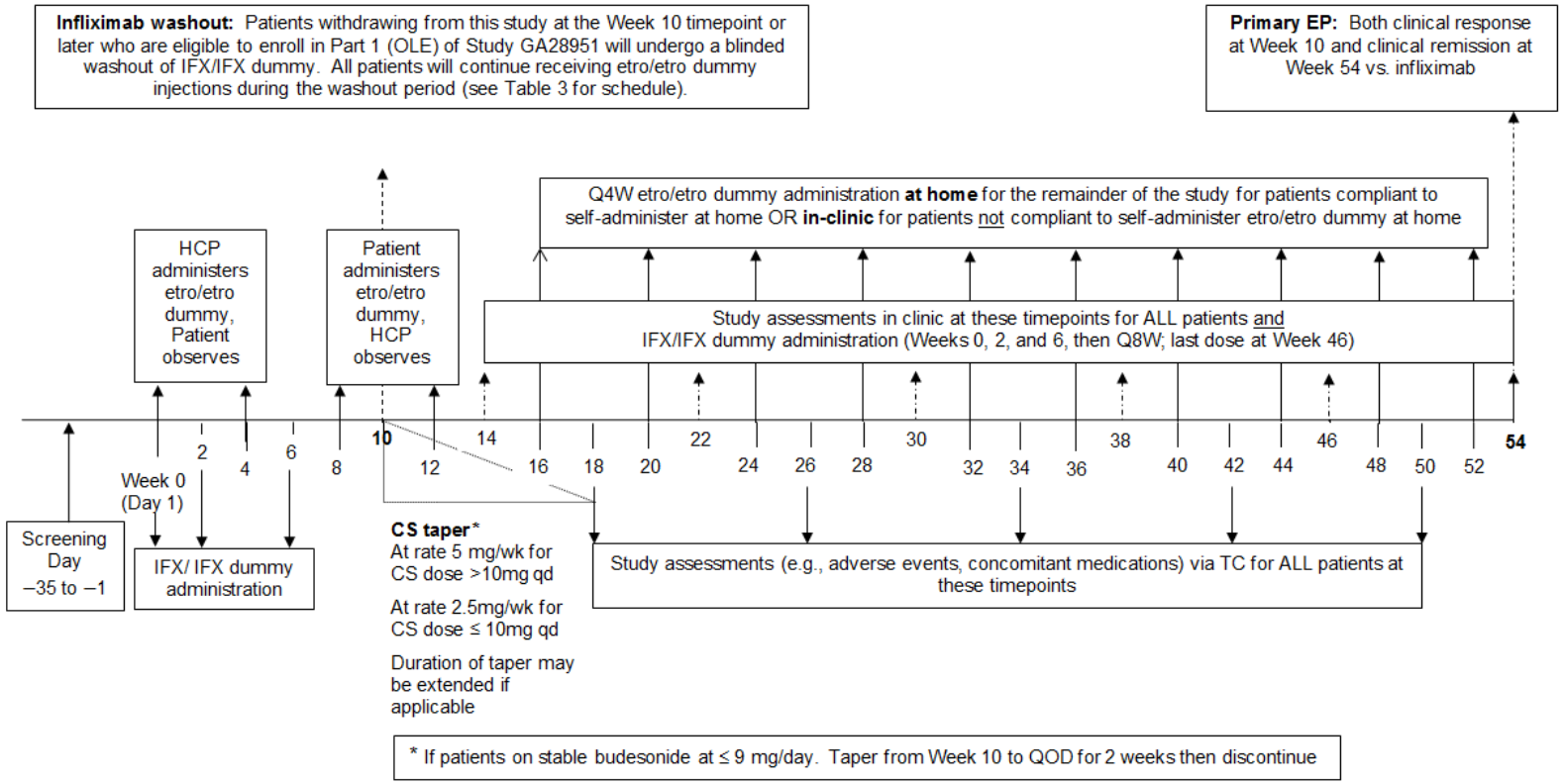
The IxRS will also make infliximab/infliximab dummy treatment assignments at Weeks 0, 2, and 6 and then at 8-week intervals until Week 46. An unblinded pharmacist will reconstitute and then dilute the infliximab to a dose of 5 mg/kg and a total volume of 250 mL with sterile 0.9% sodium chloride for infusion to patients on active infliximab. Patients randomized to infliximab dummy will be administered 250 mL sterile 0.9% sodium chloride infusion.

Patients, all study site personnel (except the unblinded pharmacist or designee responsible for infliximab accountability), the Sponsor, and its agents (with the exception of the IxRS service provider and laboratory personnel responsible for the PK sample analysis) will be blinded to treatment assignment throughout the 54-week double-blind treatment period. As described in Section 6, treatment assignment will be unblinded to the Sponsor personnel performing the analysis when all data through Week 54 are in the database and the data have been cleaned and verified and the database is locked. Personnel responsible for performing PK assays will be unblinded to patients' randomized treatment assignments in order to identify appropriate dilutions of PK samples to be analyzed. Patients and all study site personnel (except unblinded pharmacist or designee) will remain blinded to individual treatment assignment until after the study is completed (after all patients have either completed the active-treatment and safety follow-up period or discontinued early from the study) and the database is locked.

If unblinding is necessary for patient management (in the case of a serious adverse event), the investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wishes to know the identity of the study drug for any other reason, he or she

should contact the Medical Monitor. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event as per health authority reporting requirements). The Sponsor Safety Reporting Department (independent from the study team) will break the treatment code for all unexpected serious adverse events (see Section 5.2.2) that are considered by the investigator to be related to study drug for the purpose of regulatory reporting. The study team will remain blinded to study treatment.

Figure 3 Schedule of Study Drug Administration



CS = corticosteroid; EP = endpoint; Etro = etrolizumab; HCP = health care professional; IFX = infliximab; OLE–SM = open-label extension–safety-monitoring study; Q4W = every 4 weeks; Q8W = every 8 weeks; qd = once a day; QOD = every other day; TC = telephone call; Wk = week.

4.3 STUDY MEDICATION BLINDED WASHOUT OF INFLIXIMAB

Prior to switching to Study GA28951, eligible patients (see Section 4.7.2.3.1 for eligibility criteria for switch to open-label treatment) are to undergo a blinded washout period of 6 or 8 weeks (see Table 3) measured since the last infusion of infliximab/infliximab dummy. This is required to ensure adequate washout of infliximab in those patients randomized to active infliximab. During this washout, all patients will remain on blinded SC study medication (etrolizumab or etrolizumab dummy) and blinded IV study medication (infliximab/infliximab dummy) will cease. Consequently, patients randomized to active etrolizumab will continue to receive etrolizumab and patients randomized to active infliximab will continue to receive etrolizumab dummy during the blinded washout period.

The evaluation of eligibility for Part 1 (OLE) of Study GA28951 can be made at study visits, telephone contacts, and/or unscheduled visits. If eligible, the decision to switch to (but not necessarily enter) Part 1 (OLE) of Study GA28951 can occur at any timepoint listed in Column 2 of Table 3, with the earliest timepoint being the Week 10 visit, and occurring every week up to Week 52. The assessments listed for “Unscheduled Visit/Decision to Switch to OLE” should be followed (see Appendix 1). The earliest timepoint for entry into Part 1 (OLE) of Study GA28951is at the Week 12 visit and the latest is at the Week 54 visit. Due to the washout period, entry into Study GA28951 may be delayed by up to 5 weeks from the visit date at which the decision to switch is made, and detailed scenarios are outlined in Table 3.

During the blinded washout period, rescue therapy with corticosteroids (IV, oral, or topical) and/or immunosuppressants (AZA, 6-MP, or MTX) for worsening UC is permitted at the discretion of the investigator. Addition of or increases in doses of 5-ASA (oral or topical) will also be permitted per the investigator’s discretion.

At the end of the washout period, patients are to have early withdrawal/end of washout assessments AND NOT their scheduled clinic visit/telephone contact assessments prior to enrollment into Part 1 (OLE) of Study GA28951 (see Appendix 1). The first open-label dose of etrolizumab in Part 1 (OLE) ofStudy GA28951 can be administered on the same day, or at Week 54, as long as they remain eligible for Part 1 (OLE) ofStudy GA28951. Patients will be required to attend the clinic at the timepoint of Day 1 of Study GA28951 (and thereafter in accordance with the Study GA28951 protocol) and unused medication that has been given to them as part of this study is to be returned to the study site.

A complete list of study visits and assessments can be found in the Schedule of Assessments (see Appendix 1). A complete list of eligibility for enrollment of patients into Part 1 (OLE) of Study GA28951 is in Table 5.

Table 3 IFX Washout and Timing of Enrollment into Part 1 (OLE) of Study GA28951

IFX/IFX Dummy Dose Last Administered On	Decision to Switch to OLE Visit	Next Expected Dose of Etrolizumab/Etrolizumab Dummy	End of Washout Visit/Enrollment into Part 1(OLE) with 1st Administration of Open-Label Etrolizumab
Week 6	Week 10	NA	Week 12
Week 6	Week 11	NA	Week 12
Week 6	Week 12	NA	Week 12
Week 6	Week 13	NA	Week 14
Week 6	Week 14	NA	Week 14
Week 14	Week 15	Week 16	Week 20
Week 14	Week 16	Week 16	Week 20
Week 14	Week 17	Week 16	Week 20
Week 14	Week 18	NA	Week 20
Week 14	Week 19	NA	Week 20
Week 14	Week 20	NA	Week 20
Week 14	Week 21	NA	Week 22
Week 14	Week 22	NA	Week 22
Week 22	Week 23	Week 24	Week 28
Week 22	Week 24	Week 24	Week 28
Week 22	Week 25	Week 24	Week 28
Week 22	Week 26	NA	Week 28
Week 22	Week 27	NA	Week 28
Week 22	Week 28	NA	Week 28
Week 22	Week 29	NA	Week 30
Week 22	Week 30	NA	Week 30
Week 30	Week 31	Week 32	Week 36
Week 30	Week 32	Week 32	Week 36
Week 30	Week 33	Week 32	Week 36
Week 30	Week 34	NA	Week 36
Week 30	Week 35	NA	Week 36
Week 30	Week 36	NA	Week 36
Week 30	Week 37	NA	Week 38
Week 30	Week 38	NA	Week 38
Week 38	Week 39	Week 40	Week 44
Week 38	Week 40	Week 40	Week 44
Week 38	Week 41	Week 40	Week 44

Table 3 IFX Washout and Timing of Enrollment into Part 1 (OLE) of Study GA28951 (cont.)

Week 38	Week 42	NA	Week 44
Week 38	Week 43	NA	Week 44
Week 38	Week 44	NA	Week 44
Week 38	Week 45	NA	Week 46
Week 38	Week 46	NA	Week 46
Week 46	Week 47	Week 48	Week 52
Week 46	Week 48	Week 48	Week 52
Week 46	Week 49	Week 48	Week 52
Week 46	Week 50	NA	Week 52
Week 46	Week 51	NA	Week 52
Week 46	Week 52	NA	Week 52

IFX = infliximab; NA = not applicable; OLE = open-label extension.

During the blinded washout period, rescue therapy with corticosteroids (IV, oral, or topical) and/or immunosuppressants (AZA, 6-MP, or MTX) for worsening UC is permitted at the discretion of the investigator. Addition of or increases in doses of 5-ASA (oral or topical) will also be permitted if clinically indicated by the investigator.

4.4 STUDY TREATMENT

Table 4 Study/Concomitant Background Treatments

	Treatment
Investigational medicinal products	
Test product	Etrolizumab, 105 mg SC Q4W
Comparators and placebo	Infliximab, 5 mg/kg IV Weeks 0, 2, and 6, then Q8W Etrolizumab dummy, SC Q4W Infliximab dummy, IV Weeks 0, 2, and 6, then Q8W
Non-investigational medicinal products	
Concomitant background treatment	To Week 10 continuation of stable doses of the following: 5-ASA (oral); AZA; 6-MP; MTX Corticosteroid up to 30 mg/day of prednisone (or equivalent) Budesonide up to 9 mg/day At Week 10, for patients on corticosteroids at doses > 10 mg/day (prednisone equivalents), the dose should be reduced at a rate of 5 mg/week until a 10-mg/day dose is reached. For patients receiving prednisone at doses ≤ 10 mg/day (or equivalent) or once a 10-mg/day dose (or equivalent) is achieved by tapering, the dose should be reduced at a rate of 2.5 mg/week until discontinuation. Patients receiving budesonide at study entry who achieve clinical response at Week 10 are to taper their dose starting from Week 10 from 9 mg every day to 9 mg every other day for 2 weeks and then to discontinue budesonide treatment. Should patients have increased disease activity during the taper period, corticosteroid dose may be increased up to the dose at study entry if required, but tapering must begin again within 2 weeks.

5-ASA = 5-aminosalicylate; 6-MP = 6-mercaptopurine; AZA = azathioprine; IV = intravenous; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; OLE-SM = open-label extension–safety monitoring; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous; UC = ulcerative colitis.

Table 4 Study/Concomitant Background Treatments (cont.)

	Treatment
Throughout study	Throughout the study, immunosuppressants (AZA, 6-MP, or MTX) are to be maintained at the stable baseline dose unless dose reduction or discontinuation is required due to toxicity. 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 remains at the discretion of the investigator. Probiotics and oral 5-ASA may be continued at a stable dose throughout. Occasional use of NSAIDs and acetaminophen for headache, arthritis, myalgias, menstrual cramps, and daily use of low-dose (up to 325 mg daily) aspirin for cardiovascular prophylaxis are permitted. Antidiarrheals (e.g., loperamide, diphenoxylate with atropine) for control of chronic diarrhea.
During washout period prior to entering OLE–SM	During the blinded washout period, rescue therapy with corticosteroids (IV, oral, or topical) and/or immunosuppressants (AZA, 6-MP, or MTX) for worsening UC is permitted at the discretion of the investigator. Addition of or increases in doses of 5-ASA (oral or topical) will also be permitted if clinically indicated by the investigator.

5-ASA = 5-aminosalicylate; 6-MP = 6-mercaptopurine; AZA = azathioprine; IV = intravenous; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; OLE-SM = open-label extension–safety monitoring; SC = subcutaneous; UC = ulcerative colitis.

4.4.1 Formulation, Packaging, and Handling

4.4.1.1 Etrolizumab and Etrolizumab Dummy

Etrolizumab will be supplied by the Sponsor as a liquid formulation in PFSs and is administered as an SC injection. Each 1-mL PFS will contain 105 mg of etrolizumab (0.7 mL nominal volume of 150 mg/mL solution). 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.

Drug product composition for the etrolizumab dummy is identical to active drug product without the presence of etrolizumab.

Study drug packaging will be overseen by the Sponsor's clinical trial supplies department and will be 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. [redacted] In the home setting, patients should be instructed to contact the study site staff for a replacement.

Used PFS 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.

4.4.1.2 Infliximab and Infliximab Dummy

Each infliximab vial contains 100 mg of lyophilized infliximab antibody in a 20-mL vial for IV use. An unblinded pharmacist will reconstitute and then dilute the infliximab to a dose of 5 mg/kg and a total volume of 250 mL with sterile 0.9% sodium chloride for infusion.

Infliximab dummy will consist of 250 mL sterile 0.9% sodium chloride for infusion and will not be provided by the Sponsor.

Study drug packaging will be overseen by the Sponsor's clinical study supplies department and have a label 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 unblinded pharmacist or designee should check the infliximab vials for damage and verify proper identity, quantity, integrity of seals, and temperature conditions and report any deviations or product complaints to the monitor upon discover. Infliximab is to be maintained out of view of blinded study staff.

The study drug must be stored according to the details on the product label. The drug label indicates the storage temperature. Vials of study medication should be refrigerated at 2°C–8°C and protected from excessive light and heat. Vials should not be frozen, shaken, or stored at room temperature.

For further details, see the Infliximab SmPCs.

4.4.1.3 Concomitant Background Treatment for Ulcerative Colitis

For concomitant background treatment for UC see Table 4.

For further details, refer to respective SmPCs or product labels, local prescribing dosage, administration, and compliance information for the formulation, packaging, and handling details of agents prescribed as concomitant background treatment for UC.

4.4.2 Dosage, Administration, and Compliance

During the double-blind period of 54 weeks, all patients will receive two study treatments, either active etrolizumab + infliximab dummy or active infliximab + etrolizumab dummy. The dummy for etrolizumab will be a matched SC placebo, and the dummy for infliximab will be an IV saline infusion.

4.4.2.1 Etrolizumab and Etrolizumab Dummy

All patients will receive one 0.7-mL injection with use of a PFS device once Q4W. The device is a 1-mL long glass syringe with a staked-in stainless steel needle. [redacted]

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 will in turn be trained in the use of the device by an HCP and an "Information for Use" leaflet. In the event that a caregiver will ultimately administer study drug to the patient in the home setting, the caregiver is to be trained. The upper arm site may be used for caregiver but not patient administration of study treatment.

For the initial four dose administrations of SC etrolizumab/etrolizumab dummy, 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 at site 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 with severe hypersensitivity reactions (e.g., stridor, angioedema, life-threatening change in vital signs) must be withdrawn from study treatment. These patients will not be eligible to receive open-label etrolizumab in Part 1 (OLE) of Study GA28951 and are to enter the 12-week safety follow-up in this study followed by enrollment in Part 2 (SM) of Study GA28951 for 92 weeks of extended PML monitoring.

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 Section 5.1.1.2) (see the Study Manual for contact information).

Following the first four drug administrations (Weeks 0–12) and, therefore, completion of the first 3-month training period in a clinical setting, study drug administration (Week 16 and then Q4W onwards) 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 patients' home after return from the clinic visit. 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 the site's source documentation. 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 7). 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. Patients will also be given information regarding the recognition of signs and 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. Following the delay, 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 (including those following an injection in the home setting) (see Section 5.1.1.3) should be documented appropriately on the adverse event electronic Case Report Form (eCRF) page. Patients administering the SC injection at home should be taught to report any injection-site reactions as adverse events (e.g., redness and/or swelling).

Guidelines for treatment interruption or discontinuation are provided in Section 4.8.

4.4.2.2 Infliximab and Infliximab Dummy

In addition to etrolizumab/etrolizumab dummy, patients will receive either infliximab (5 mg/kg IV at Weeks 0, 2, and 6, then Q8W) or infliximab dummy IV administered in the clinic setting until Week 46.

For infliximab, an unblinded pharmacist will reconstitute and then dilute the infliximab to a dose of 5 mg/kg and a total volume of 250 mL with sterile 0.9% sodium chloride for infusion. The patient will be dosed on the basis of the patient's weight at baseline.

Under aseptic conditions, reconstitute each infliximab vial with 10 mL of water for injections using a syringe equipped with a 21-gauge (0.8 mm) or smaller needle. Remove flip-top from the vial and wipe the top with a 70% alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of water for injections to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. Check that the solution is colorless to light yellow and opalescent. The solution may develop a few fine translucent particles, as infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign particles are present.

Dilute the total volume of the reconstituted infliximab solution dose to 250 mL with sodium chloride 9 mg/mL (0.9%) solution for infusion. This can be accomplished by withdrawing a volume of the sodium chloride 9 mg/mL (0.9%) solution for infusion from the 250-mL glass bottle or infusion bag equal to the volume of reconstituted infliximab. Slowly add the total volume of reconstituted infliximab solution to the 250-mL infusion bottle or bag. Gently mix.

The infusion is to be administered over a period of not less than 2 hours. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 1.2 μm or less). Since no preservative is present, it is recommended that the administration of the solution for infusion is to be started as soon as possible and within 3 hours of reconstitution and dilution. When reconstitution and dilution are performed under aseptic conditions, infliximab infusion solution can be used within 24 hours if stored at 2°C–8°C. Do not store any unused portion of the infusion solution for reuse.

No physical biochemical compatibility studies have been conducted to evaluate the co-administration of infliximab with other agents. Do not infuse infliximab concomitantly in the same IV line with other agents.

Visually inspect infliximab for particulate matter or discoloration prior to administration. Do not use if visibly opaque particles, discoloration, or foreign particles are observed.

Any unused product or waste material should be disposed of in accordance with local requirements.

The infliximab dummy infusion will consist of 250 mL sterile 0.9% sodium chloride injection and will also be administered over a period of not less than 2 hours.

Patients will be monitored during infusion and for 1 to 2 hours after the infusion. Patients and investigators will remain blind to the infliximab study treatment.

The patient is to be provided with the alert card for infliximab.

For guidelines for dosage modification and treatment interruption or discontinuation, refer to the Infliximab Investigator's Brochure and infliximab SmPC.

4.4.2.3 Concomitant Background Treatment and Rescue Therapy

Patients must have had an inadequate response, loss of response, or intolerance to prior immunosuppressant and/or corticosteroid treatment, as described in Section 4.1.1 and as described below.

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

- Persistent signs and symptoms of active disease despite a history of at least one 12-week regimen of oral AZA (≥ 1.5 mg/kg) or 6-MP (≥ 0.75 mg/kg) and/or MTX (≥ 15 mg/week) within the previous 5 years
- Persistent signs and symptoms of active disease despite a 6-TG level of ≥ 230 pmol/8 $\times$108 RBCs during at least one 12-week regimen of oral AZA or 6-MP at a stable or increasing dose within the previous 5 years
- History of intolerance to AZA, 6-MP, or MTX (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, LFT abnormalities, lymphopenia, *TPMT* genetic mutation, infection) within the previous 5 years

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

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

Management of Concomitant Medications during the Study

During Induction Phase (Prior to Week 10):

Patients are required to maintain stable doses of their concomitant medications (oral 5-ASA, corticosteroids, immunosuppressants) for UC.

During Maintenance Phase (After Week 10)

Corticosteroids

Patients on corticosteroids from baseline must begin the specified corticosteroid taper at Week 10. Patients receiving prednisone at a dose of >10 mg/day (or equivalent) are to have their dose reduced at a rate of 5 mg per week until a 10 mg/day dose is achieved. Patients receiving prednisone at doses ≤ 10 mg/day (or equivalent), or once a 10 mg/day dose (or equivalent) is achieved by tapering, are to have their dose reduced at a rate of 2.5 mg/week until discontinuation. Patients receiving budesonide at study entry should taper their dose of 9 mg every day to 9 mg every other day for 2 weeks and then discontinue budesonide treatment. For patients who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms of either UC or steroid withdrawal, corticosteroid dose may be increased (up to the dose at study entry, if required), but tapering must begin again within 2 weeks. An increase in corticosteroid dose back to baseline is not considered rescue medication if it occurs during the corticosteroid taper. These patients should remain in the study.

Immunosuppressants

Patients should remain on their stable baseline doses of immunosuppressants (AZA, 6-MP, MTX) throughout the study unless dose reduction or discontinuation is required because of a toxicity related to the medication (see Section 3.1.1 for symptoms of toxicity to AZA, 6 MP, or MTX).

Rescue Therapy That Can Be Given with Study Medication for the Treatment of Ulcerative Colitis

During the Induction Phase (Prior to Week 10):

Patients are required to maintain stable doses of their concomitant medications (5-ASA, corticosteroids, immunosuppressants) for UC.

In the Induction Phase, any patient who requires initiation of an immunosuppressant (AZA, 6-MP, or MTX), corticosteroid, or oral or topical 5-ASA, or increase in dose over baseline levels for treatment of worsening disease symptoms, should stay in the blinded study. These patients will be considered non-responders for the Induction timepoint.

During the Maintenance Phase

Initiation or escalation of oral 5-ASA should be avoided but is permitted if deemed clinically necessary by the investigator. Patients who initiate or escalate oral 5-ASA therapy should continue blinded treatment.

Use of topical or IV corticosteroids or topical 5-ASA should also be avoided as concomitant medication. However, if these are clinically required to treat symptoms of

UC, then the patient may either remain in the blinded phase of the study or be given the option to enroll in Part 1 (OLE) of Study GA28951, if eligible, based on the investigator's discretion and after completion of the washout phase (see Table 3), including the decision to switch to OLE visit and early withdrawal/end of washout visit (see Appendix 1).

Patients who were not receiving corticosteroids at baseline and patients who have completed the steroid taper who subsequently receive oral corticosteroids at a dose greater than 10 mg for 5 days or longer for the treatment of worsening UC symptoms or steroid withdrawal may remain in the blinded study or may be given the option to enroll in Part 1 (OLE) of Study GA28951, if eligible, based on the investigator's discretion and after completion of the washout phase (see Table 3), including the decision to switch to OLE visit and the early withdrawal/end of washout visit (see Appendix 1).

Immunosuppressants (AZA, 6-MP, or MTX): Patients are to remain on their stable baseline dose of immunosuppressant therapy throughout the study unless dose reduction or discontinuation is required due to toxicity. 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 remains at the discretion of the investigator. Patients who do initiate or escalate immunosuppressant therapy may remain in the blinded study or may be given the option to enter Part 1 (OLE) of Study GA28951, if eligible, based on the investigator's discretion and after completion of the washout phase (see Table 3), including the decision to switch to OLE visit and the early withdrawal/end of washout visit (see Appendix 1).

Endoscopy to document disease activity for patients exiting the treatment period early for any reason *may be performed at the discretion of the investigator.*

Rescue Therapy That Cannot Be Given with Study Medication for the Treatment of UC

At ANY time during the conduct of the study, use of other immunosuppressive agents including, but not limited to, anti-integrins, T- or B-cell depleters (except AZA and 6-MP), TNF inhibitors (including TNF inhibitor biosimilars),cyclosporine, tacrolimus, anti-adhesion molecules, *JAK inhibitors*, or investigational agents are prohibited. Use of anakinra, abatacept, tocilizumab, and other biological therapeutics are also prohibited.

Patients who receive such therapies are not to receive further study treatment or open-label treatment, and will be required to enter 12 weeks of safety follow-up in this study (see Appendix 2). After completion of safety follow-up, these patients will be requested to enroll in Part 2 (SM) of Study GA28951 for 92 weeks of extended PML monitoring.

4.4.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (etrolizumab, etrolizumab dummy, and infliximab, will be provided by the Sponsor. Infliximab dummy is saline (sodium chloride 9 mg/mL [0.9%]) solution for infusion and will not be provided. 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. 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. Note that infliximab accountability and storage will be conducted by an unblinded study staff member. Infliximab study drug will not be available to blinded study staff.

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.

4.4.4 Assessment of Compliance

Etrolizumab

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

Etrolizumab/etrolizumab dummy home injection: An e-diary will be provided to patients to record home injections.

Patients will be asked to return all unused PFSs in the provided boxes at each visit as a measure of drug accountability and patient compliance. Site personnel will monitor the medication records from the e-diary via an online portal. However, patients should also bring their e-diary to the clinic during 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 4.4.3. The investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator. When the study is completed, the investigator will return all completed Drug Dispensing Logs to the Monitors.

Any unused study drug and Drug Return Records should be returned to the Monitor, unless alternate destruction has been authorized by Roche or required by local or institutional regulations (see Section 4.4.3). The investigator's copy of the Drug Return Record(s) must accurately document the return of all study drug supplies to Sponsor.

Infliximab

A Drug Dispensing Log must be kept as described in Section 4.4.3. The blinded study staff are responsible for ensuring that dosing is administered in compliance with the protocol. When the study is completed, the study staff will return all completed Drug Dispensing Logs to the Monitors.

Any unused study drug and Drug Return Records should be returned to the Monitor, unless alternate destruction has been authorized by Roche or required by local or institutional regulations (see Section 4.4.3). The investigator's copy of the Drug Return Record(s) must accurately document the return of all study drug supplies to Sponsor.

4.4.5 Destruction of the Investigational Medicinal Product

Any used etrolizumab/etrolizumab dummy PFS will be placed into sharps containers immediately after SC injections either at site or at home. Any used needles for infliximab infusion will be placed into sharps containers immediately after completion of infusion period at the site. 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 etrolizumab/etrolizumab dummy PFS should not be destroyed, and instead should be returned to the investigator site in the packaging provided for this purpose. The device is to be sent from the investigator site to the appropriate Sponsor’s clinical trial supplies department for further assessment (see Section 4.4.3).

4.4.6 Reporting of Prefilled Syringe Complaints/Events

The investigator should report all medical device complaints to the Sponsor. The investigator must document as much information as possible on the PD103 IMP deviation form, including product batch number and expiration date, and forward the complaint form to the Sponsor 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 necessary.

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 5.4.2. 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 as a spontaneous adverse event to the Sponsor (see Section 5.3.5).

4.5 CONCOMITANT THERAPY

4.5.1 Permitted 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 8 weeks prior to randomization (Day 1) to the study completion/early termination visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

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

For concomitant therapy for UC and rescue treatment see Section 4.4.2.3.

4.5.2 Prohibited Therapy

Use of the following therapies is prohibited during the study:

- Any investigational treatment including investigational vaccines
- Use of lymphocyte-depleting agents (e.g., alemtuzumab or visilizumab), except for agents such as AZA and 6-MP
- Use of cyclosporine, tacrolimus, sirolimus, or MMF
- Use of natalizumab, vedolizumab, or rituximab

- Use of TNF-inhibitors (including TNF inhibitor biosimilars) other than infliximab (study drug)
- Use of anakinra, abatacept, tocilizumab, and other biological therapeutics
- Use of anti-adhesion molecules
- *Use of JAK inhibitors*

Patients who receive these specified rescue therapies are not to receive further study treatment or open-label treatment and are to be discontinued from study drug and entered into safety follow-up within this study.

4.6 DISEASE WORSENING

4.6.1 Definition of Disease Worsening

Disease worsening is defined as:

- An increase in the pMCS ≥ 3 points from Week 10 AND an absolute pMCS ≥ 5 AND an endoscopy subscore of ≥ 2
- OR absolute pMCS ≥ 7 AND an endoscopy subscore of ≥ 2

If a patient meets criteria for disease worsening during the Maintenance Phase of the study (Week 10 to Week 54), he or she may withdraw from this study and enroll in Part 1 (OLE) of Study GA28951, if eligible, after a brief washout phase to receive open-label etrolizumab.

4.7 STUDY ASSESSMENTS

4.7.1 Description of Study Assessments

4.7.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases and procedures. All medication taken in the 8 weeks prior to randomization (Day 1) (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies) are to be recorded. A detailed history of medication used for UC is required for the 5 years prior to screening.

Demographic data including age, sex, whether the patient is a fraternal or identical twin, and self-reported race/ethnicity will be collected during the screening period.

4.7.1.2 Physical Examinations

A complete physical examination should include the evaluation of head, eye, ear, nose, and throat, and cardiovascular, dermatological, musculoskeletal, respiratory, GI, and neurologic systems, including administration of the PML Subjective Checklist and the PML Objective Checklist by the investigator (see Appendix 5 for PML assessment details and Appendix 6 for PML algorithm). New or worsened abnormalities from screening should be recorded as adverse events if appropriate. In addition, a symptom-driven examination should be conducted as indicated in the Schedule of Assessments (see Appendix 1 and Appendix 2).

4.7.1.3 Vital Signs

Vital signs will include measurement of heart rate and systolic and diastolic blood pressure, after the patient has been in a seated position for 5 minutes, and are to be recorded before study drug administration at clinic visits only at the indicated timepoints in Schedule of Assessments (see Appendix 1).

4.7.1.4 Ulcerative Colitis Disease Activity Assessments

Extent and duration of patient's disease is to be recorded on the eCRF from the patient medical records and should include therapies from the last 5 years. Extent of disease should be defined as follows: 1) left-sided colitis (up to the splenic flexure), 2) extensive colitis (beyond the splenic flexure but not involving the entire colon), and 3) pancolitis.

All measurable disease must be documented at screening and re-assessed at each subsequent evaluation. Responses will be assessed by the investigator or designee with use of the MCS and pMCS. The MCS has a range of 0–12, whereas pMCS has range 0–9, with higher scores indicating more severe disease. MCS is a composite of four assessments, each rated from 0–3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment (PGA). pMCS is a composite of three assessments, each rated from 0–3: stool frequency, rectal bleeding, and PGA.

During screening, patients will be instructed on how to appropriately use and complete questions on the e-diary. The patients' normal number of stools is to be recorded. This is defined as the number of stools 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.

One of the components of the MCS is the endoscopic subscore. The time window for performing endoscopy during the screening is 4–16 days prior to randomization (Day 1) (i.e., Day − 16 to Day − 4). Medical Monitor approval is not required for endoscopies conducted within this window. Under no circumstances will an endoscopy be accepted more than 16 days or less than 4 days prior to Day 1. Note that the total screening period is up to 35 days (see Section 4.7.2.1 and Appendix 4).

The symptoms of UC must be recorded throughout the study, including the screening period. The e-diary entries will be reviewed by site personnel during screening (prior to dosing, if applicable) and during study visits, including the early withdrawal/end of washout visit and any unscheduled visits due to disease exacerbation. Because the colonoscopy/flexible sigmoidoscopy and bowel cleansing preparations can 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 4.

Colonoscopy/Flexible Sigmoidoscopy with Colonic Biopsies

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

Stool samples for analysis of fecal calprotectin and other exploratory biomarkers (such as analyses of the microbiota and bacterial cultures) are to be collected prior to bowel preparation (polyethylene glycol [PEG]-based preparation or enema).

Full colonoscopy within a year of screening is required to ensure against enrollment of patients with colonic carcinoma and dysplasia. If full colonoscopy has not been performed within the year before screening, it should be conducted in place of the flexible sigmoidoscopy at screening. For patients not requiring a colonoscopy, a flexible sigmoidoscopy will be performed on all patients for inclusion in the study. Endoscopy will be performed 4-16 days prior to randomization (Day 1).

Endoscopy will be also performed at Weeks 10 and 54 and/or at unscheduled visits (including the decision to switch to OLE visit) if clinically indicated and/or at withdrawal from the study (early withdrawal visit, Appendix 1). An endoscopy is not required at the end of washout visit if an endoscopy was already performed at the decision to switch to OLE visit.

Central reading of endoscopies will be performed throughout this study and a detailed charter will address the standardization of endoscopic procedures, video recordings, and equipment, as well as the criteria for endoscopic assessment. For each patient, video recording of the entire endoscopic procedure will be performed as specified in the Video Submission Guidelines. All video recordings will be edited by central read vendor to produce video clips that are representative of each segment of the colon visualized up to the splenic flexure only (rectum, sigmoid, and descending colon). The video clips will be read centrally for mucosal lesions and endoscopic severity by an independent gastroenterologist experienced in IBD who is blind to the patient's clinical activity and treatment allocation. The MCS endoscopic subscore is to be determined both locally (at the investigator site) and centrally as described above. Each segment of the colon up to the splenic flexure (rectum, sigmoid, and descending colon) will be assigned an endoscopic subscore. The score from the worst affected segment up to the splenic flexure is to be used for the MCS calculation, *for study conduct,* except at post-baseline time points, when the sigmoid colon MCS endoscopic subscore will be used if the baseline sigmoid colon MCS endoscopic subscore is 2–3.

In the event that there is a discrepancy between the endoscopic subscore obtained by the local versus the central reader, a third read (performed by a second central reader) is to be conducted. From these three endoscopic MCS subscores, the score with which two readers agree will be reported as the final overall MCS endoscopic subscore. If no two readers agree on an MCS endoscopic subscore, the median score of the three

completed reads (i.e., local read, central read #1, and central read #2) will be chosen as the final reported overall MCS endoscopic subscore.

In all cases the video recordings are to be taken prior to biopsy.

Each patient entered into the study will have colonic biopsies obtained during flexible sigmoidoscopy/full colonoscopy as follows.

At Screening

A total of five to six paired biopsy samples (10 to 12 samples) will be taken at screening.

- Five paired biopsy samples (10 samples) from the most inflamed area of the colon within 20–40 cm from the anal verge (sigmoid colon).
  - Three pairs (6 samples) will go into formalin.
  - Two pairs (4 samples) will be placed in stabilization buffer (such as RNAlater or a similar buffer) and be shipped to a central laboratory for storage at –80°C.
  - In U.K. sites ONLY, one of the latter pair of biopsies (two samples) will be placed in storage solution and shipped at 4°C to the U.K. laboratory.
- ONLY if there is suspicion for clinically significant CMV colitis, one biopsy sample should be taken from the base of an ulcer to evaluate for histological presence of CMV but otherwise is not necessary for inclusion in the study. Analysis should be performed locally if possible, or can be sent to a central laboratory if necessary.
- Only if histopathologic confirmation of UC is needed to meet study eligibility, an additional biopsy sample can be used for histopathologic confirmation of UC if necessary (analysis should be performed locally if possible or can be sent to a central laboratory if necessary).
- If neither CMV testing nor histopathologic confirmation of UC is needed, these additional 2 biopsy samples should not be obtained.

At Weeks 10 and 54 and/or at early withdrawal visit and/or unscheduled visits/decision to switch to OLE visit, if indicated (see Appendix 1)

Four paired biopsy samples (8 samples) will be obtained at subsequent visits, as specified in Appendix 1. Four paired biopsy samples (8 samples) are to be taken from the most inflamed area of the colon within 20–40 cm from the anal verge (sigmoid colon, approximately at the same endoscopic depth of the original screening endoscopy). If there is no clearly inflamed area, a blind biopsy should be taken.

- Two pairs will go into formalin.
- Two pairs will be placed in stabilization buffer (such as RNAlater or a similar buffer) and shipped to a central laboratory for storage at –80 C.

  In U.K. sites ONLY, one of the latter pair of biopsies (two samples) will be placed in storage solution and shipped at 4°C to the U.K. laboratory.

Necrotic areas of ulcerated mucosa should be avoided during biopsy. Original location (colonic segment and endoscopic depth) of biopsy specimen should be clearly indicated. Samples will all initially be sent to the laboratory vendor (unless analysis is to be performed locally, as indicated).

Progressive Multifocal Leukoencephalopathy Assessment

Study site personnel and patient 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 (see Appendix 5) by a qualified HCP and will be performed at screening and as indicated on the Schedule of Assessments.

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 5.2 and Appendix 6 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 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 study treatments can be resumed only in patients where PML has been ruled out. See Appendix 6 for the Algorithm for Evaluation of Progressive Multifocal Leukoencephalopathy.

After completing the treatment phase of the study, patients not enrolling in Part 1 (OLE) of Study GA28951 to receive treatment with open-label etrolizumab will enter the 12-week safety follow-up in this study (see Appendix 2). The PML neurologic examination is to be performed at Week 12 of this safety follow-up.

Following 12-week safety follow-up, all patients will be requested to continue to be monitored for PML for an additional 92 weeks by enrolling in Part 2 (SM) of Study GA28951, thus providing a total of 2 years PML follow-up after the last dose of study medication. During Part 2 (SM) of Study GA28951, patients will not be administered study drug.

The PML extended follow-up period in Study GA28951 will consist of the PML assessment interview conducted by telephone at 6-month intervals.

4.7.1.5 Laboratory Assessments

Laboratory assessments will be performed as indicated on the Schedule of Assessments; see the Study Flowchart in Appendix 1. All laboratory investigations will be sent to one or more central laboratories for analysis with the exception of CMV. If there is suspicion for clinically significant CMV colitis, a colonic biopsy sample should be sent for CMV evaluation, which may be conducted locally depending on local requirements for the timing of the test result. Urine pregnancy testing will also be conducted locally or in the home setting. If a full colonoscopy is required at screening, laboratory samples should be drawn prior to the initiation of bowel preparation.

On days of study drug administration, laboratory samples should be drawn before the administration of study drug. 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 RBC distribution width)
- Serum chemistries, including liver function test (sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatine phosphokinase, and uric acid)
- Urinalysis
- Tuberculosis

  The PPD skin test and QuantiFERON–TB Gold are acceptable screening assays for latent *Mycobacterium* TB infection.

  A positive PPD tuberculin skin test reaction is considered ≥ 5 mm

  Patients with a history of bacille Calmette-Guérin (BCG) vaccination should be screened using the QuantiFERON-TB Gold test only.

  An indeterminate QuantiFERON-TB Gold test should be repeated. The follow-up test can be either a repeat of the previous test or a PPD tuberculin skin test in patients who are eligible to have a PPD tuberculin skin test performed.

The patient is considered to have a **positive** diagnostic test for TB if at least one of the following circumstances applies:

- A positive QuantiFERON-TB Gold test
- Two successive indeterminate QuantiFERON-TB Gold tests
- A positive PPD tuberculin skin test

The patient is considered to have a **negative diagnostic test** for TB if at least one of the following circumstances applies:

- A negative QuantiFERON-TB Gold test
- A negative PPD tuberculin skin test

If a negative TB screening test has been documented within 3 months of screening, no new test is needed.

- JCV antibodies

  A plasma sample to test for antibodies to JCV will be taken and stored for possible later assessment of how widespread the JCV infection is in the study population. Sample testing for the presence of JCV antibodies is not helpful in predicting risk for PML or for evaluating neurologic symptoms. The sample may be tested if there is a strong belief that this information will be helpful in managing a patient's condition.

- C-reactive protein (CRP)
- *C. difficile* toxin assay in stool, stool culture and sensitivity testing, and stool ova and parasites analysis
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening.

  Urine pregnancy tests will be performed at specified subsequent visits either in the clinic or in the home setting. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

- Viral serology and detection

  HBV (HBsAg, total HB core antibody [anti-HBc] and HBV DNA)

  HCV antibody

  HCV RNA: Measurement of HCV RNA with use of the Amplicor assay is required when the patient has a known history of HCV antibody positivity with past documentation of undetectable HCV RNA, either with or without history of anti-viral treatment. Patients with newly diagnosed HCV antibody positivity are not eligible for this study, and therefore do not require measurement of HCV RNA.

  HIV

- Anti-therapeutic antibody (ATA) assays

  Serum samples will be collected in subset of patients for the detection and characterization of antibodies against etrolizumab, or if necessary, infliximab. Samples will be analyzed using a validated assay if possible. For ATA samples without matched PK determinations, etrolizumab or infliximab concentrations may be measured for the purpose of helping interpret ATA data. ATA samples may also be utilized for exploratory PD biomarkers.

- PK assays

  Serum samples will be collected from 400 patients at selected sites for potential determination of etrolizumab concentrations. Separate informed consents will be required for these 400 patients for this PK sample. Samples will be analyzed using a validated assay.

- CMV testing of colonic biopsy if there is suspicion for clinically significant CMV colitis

  Baseline colon biopsy (to be obtained at the base of the ulcer) will be analyzed for histologic presence of CMV

- Fecal calprotectin testing

- Exploratory *predictive and prognostic* biomarker assays

  Peripheral blood, serum, and colon biopsy samples will be assessed using qualified methods (including, but not limited to, ELISA, IHC, and/or qPCR*, RNA sequencing,*) for exploratory *predictive and prognostic* biomarker analysis.

- Exploratory PD biomarker assays

  Peripheral blood, stool, and serum samples will be collected from a subset of patients at designated sites (see Appendix 1 for samples to which this applies). Colon biopsy sample will be collected from all patients.

  Peripheral blood, serum, stool, and colon biopsy samples will be collected for exploratory PD biomarker analysis. For samples that are to be assessed, qualified methods, including, but not limited to, ELISA, IHC, bacterial culture*, RNA sequencing*, and/or qPCR will be utilized. Biopsy tissue may also be used for exploratory determination of drug concentration. Stool samples may be used for assessments that include, but are not limited to, analyses of the microbiota and bacterial cultures.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.7.1.10), 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.

- Blood *or blood-derived* samples (RNA Paxgene, serum for exploratory PD) and stool samples collected for biomarker research 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.

4.7.1.6 Chest X-Ray

A chest X-ray will be performed at screening. If a chest X-ray has been documented within the previous 3 months and has shown no clinically significant abnormalities, no additional chest X-ray is required.

4.7.1.7 Electrocardiograms

Electrocardiograms (ECGs) for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to meals and any scheduled vital sign measurements and blood draws.

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

4.7.1.8 Patient-Reported Outcomes

Patient-reported outcomes (PROs) (IBDQ, EQ-5D, and the stool frequency and rectal bleeding components of the MCS and pMCS), physician-reported outcomes (PGA component of the MCS and pMCS), and the endoscopic component of MCS data will be collected to help characterize the clinical profile of etrolizumab. The instruments will be translated as required in the local language.

In order to ensure instrument validity and that data standards meet health authority requirements, the PROs completed at the sites (IBDQ, EQ-5D, and the stool frequency and rectal bleeding components of the MCS and pMCS) should be administered at the investigational site prior to the completion of non-PRO assessments and before the patient receives any disease-status information or study drug during that visit. At Week 0 (Day 1), however, IBDQ and EQ-5D do not have to be performed prior to non-PRO assessments. Patients will complete the stool frequency and rectal bleeding components of the MCS daily from the first screening visit for the patient throughout the study.

PRO data will be collected electronically using electronic patient-reported outcome (ePRO) devices (i.e., e-diary or tablet). The format of the questionnaires may change when they are converted to electronic format. Electronic data captured by the patient

since the previous study visit should be reviewed with the patient at each clinic visit. ePRO data will be collected and assessed at visits according to the Schedule of Assessments in Appendix 1.

Inflammatory Bowel Disease Questionnaire

The IBDQ will be used to assess patients' health-related QOL (Guyatt et al. 1989; Irvine 1999). The 32-item questionnaire contains four domains: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items). The items are scored on a 7-point Likert scale with a higher score indicating better health-related QOL. The IBDQ has a recall specification of 2 weeks. A copy of the IBDQ is provided in Appendix 9.

Mayo Clinic Score (MCS) and Partial Mayo Clinic Score (pMCS)

The MCS is a composite of four assessments, each rated from 0–3: stool frequency, rectal bleeding, endoscopy, and PGA (Schroeder et al. 1987). The endoscopy subscore of the MCS is derived from an evaluation of findings on endoscopy as determined by the central reading procedure described in Section 4.7.1.4. The pMCS is a composite of three assessments, each rated from 0–3: stool frequency, rectal bleeding, and PGA. The MCS has a range of 0–12 and the pMCS has a range of 0–9. Higher scores indicate more severe disease. Copies of the MCS and pMCS scoring system are provided in Appendix 4.

EuroQol Five-Dimension Questionnaire

The EQ-5D is a generic preference-based health-related QOL questionnaire that provides a single index value for health status (Rabin and deCharro 2001). This tool includes questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that are used to build a composite of the patient's health status. The EQ-5D questionnaire will be utilized in this study for economic modeling. A copy of the assessment is provided in Appendix 10.

4.7.1.9 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.

4.7.1.10 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. In addition, any residual colonic biopsy and blood samples for biomarkers left over at the end of the study and analyses 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 Institutional Review Board or Ethics Committee (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

Whole blood (DNA) will be collected for genetic analysis from consenting patients (RCR ICF).

Samples that are obtained for exploratory analysis of biomarkers (listed below) but were not utilized or were not entirely consumed will be transferred to the RCR.

Specimen types include the following:

- Blood collected in RNA Paxgene tubes (for exploratory PD; see Appendix 1 for specific collection timepoints)
- Serum for exploratory PD (see Appendix 1 for specific collection timepoints)
- Stool samples may be used for exploratory biomarker analyses (see Appendix 1 for specific collection timepoints)
- Colon biopsy samples (formalin and stabilization buffer [such as RNAlater or a similar buffer]; see Appendix 1 for specific collection timepoints)

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).

All 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 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.

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 GA29103 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 GA29103.

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.

4.7.2 Timing of Study Assessments

4.7.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for randomized patients and for patients who are not subsequently randomized will be maintained at the study site.

All screening tests and evaluations will be performed within 35 days prior to randomization (Day 1) except for flexible sigmoidoscopy/colonoscopy, which should be performed 4–16 days prior to randomization (Day 1) (see Figure 4). The screening period will not exceed 35 calendar days.

Laboratory samples should be collected from the patient early in the screening period to allow time for the laboratory results to be available for review by the site for eligibility (see Section 4.7.1.4). However, the ECG and chest X-ray can be obtained any time before randomization (Day 1) to study medication (see Section 4.7.1.6 and Section 4.7.1.7 for additional details on the chest X-ray and ECG). Colon biopsy specimen collection is detailed in Section 4.7.1.4.

A blood sample to test for antibodies to JCV will be taken and stored for possible later assessment of how widespread the JCV infection is in the study population. Sample testing for the presence of JCV antibodies is not helpful in predicting risk for PML or for evaluating neurologic symptoms. The sample may be tested if there is a strong belief that this information will be helpful in managing a patient's condition.

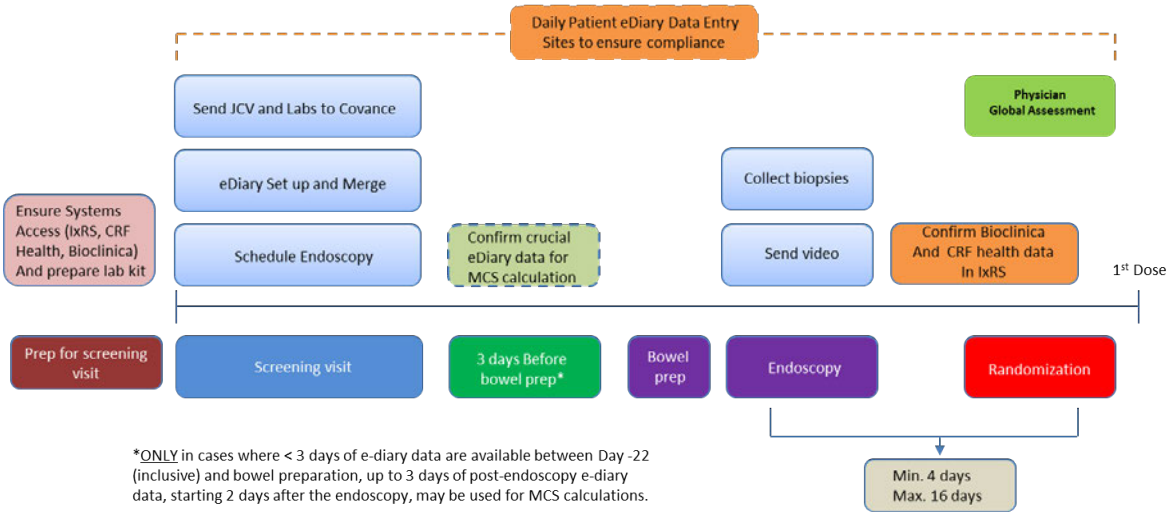
The screening endoscopy for MCS should be performed 4–16 days prior to randomization (Day 1) (i.e., Day – 16 to Day – 4). The endoscopy score from the worst affected segment up to the splenic flexure (rectum, sigmoid, and descending colon) is to be used for the MCS calculation (see Section 4.7.1.4).

The symptoms of UC must be recorded during the screening period. The e-diary entries will be reviewed by site personnel during screening. Because the colonoscopy/flexible sigmoidoscopy and bowel cleansing preparations can 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 4.

The endoscopy and stool frequency and rectal bleeding subscores will be considered, along with other PGA components, when determining the PGA for the MCS calculation at Day 1 (i.e., prior to initiation of study drug), as described in detail in Appendix 4..

Figure 4 Overview of Screening Activities



Note: Endoscopy should be performed 4–16 days prior to randomization (Day 1)

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization (Day 1). The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.7.2.1.1 Re-Testing for Laboratory Inclusion and Exclusion Criteria

Two re-tests are permitted for laboratory inclusion and exclusion criteria. If a patient does not meet laboratory criteria for a third time, he or she will be considered a screen failure.

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

4.7.2.1.2 Re-Screening

Re-screening is required if a patient has not met all the eligibility criteria within 35 days of the original screening visit. Patients who are found to be ineligible for entry into the study may be re-screened once only—for example, if the patient develops additional manifestations of UC, a worsening of existing manifestations at a later time, if patient's clinical status has changed such that the abnormal laboratory value may be directly affected (e.g., transfusion). Each patient must be re-consented before re-screening occurs.

Re-screening is not required for the HIV preliminary and confirmatory tests, HCV antibody test, and hepatitis B assessment (i.e., HBsAg, HBcAb, and, if required, HBV DNA), provided that the following criteria are met:

- Test results are available from the initial screening
- Eligibility criteria for the assessments are satisfied
- Date of the initial screening assessment was ≤6 weeks prior to the re-screening Day 1 visit (day of randomization for second screening)
- In the investigator's judgment, the patient is not deemed to have been at risk for HIV, hepatitis C, or hepatitis B infection (based on medical history, or geographical or social circumstance)

As described in Section 4.7.1.5, if a negative TB screening test result has been documented within 3 months before screening or re-screen, no repeat test is required.

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

- All endoscopy-related inclusion criteria have been met
- The initial endoscopy has been performed within 28 days prior to the day of randomization for second screening)
- Colon biopsies as specified by the protocol have been obtained

If the initial screening endoscopy does not meet the conditions outlined above, the endoscopy and protocol-specified colon biopsies should be repeated 4–16 days prior to randomization (Day 1).

Re-Screening in the Event of Screen Failure Due to *C. Difficile* or CMV Infection

Patients who are classified as screen failures due to the presence of *C. difficile* or CMV infection may be re-screened 60 days after successful treatment. For patients who screen failed due to CMV infection, laboratory analysis of CMV from colon biopsy sample is required during re-screening evaluation to rule out CMV infection.

See Appendix 1 for the schedule of screening and pretreatment assessments.

4.7.2.2 Assessments during Treatment

All assessments will be performed on the day of the specified visit, except where a time window is specified. Assessments scheduled on the day of study drug administration should be performed prior to dosing, unless otherwise noted. When study drug 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.

For visits that are associated with a MCS requiring endoscopy, every effort should be made to schedule the endoscopy on the same day as the clinic visit. If this is not possible, endoscopy should be performed as close to the clinic visit as possible, with a maximal window of 3 days prior to and 5 days after the visit. The endoscopy score should be considered when determining the PGA (as applicable), a component of the MCS (see Appendix 4).

On a number of occasions during the Maintenance Phase (see Appendix 1 and Figure 3), patients will be contacted by telephone for the purpose of study assessment, rather than making a clinic visit. During these telephone visits, data will be collected as for a clinic visit at this time with the exception of blood sample and in-clinic PRO assessments (see Appendix 1, Schedule of Assessments). All adverse events and concomitant medications will be recorded and the patient questioned regarding a potential disease worsening. An unscheduled visit is to be conducted as required (see Section 4.7.2.5).

All patients will receive hands-on training in the use of the e-diary and tablet. Patients will also be instructed to contact the site promptly if they have any questions about the use of the e-diary during screening or at any time during the study.

See Appendix 1 for the schedule of assessments performed during the treatment period.

4.7.2.3 Assessments at Study Completion/Early Withdrawal/End of Washout Visit

The completion of the study treatment period is defined as the Week 54 visit. Patients who complete the study will be asked to visit the clinic for the Week 54 assessments (see Appendix 1). If a patient leaves the study prior to Week 54, an early withdrawal/end of washout visit is to be conducted following infliximab washout, as defined in Sections 3.1.1.3 and Section 4.3. Assessments are specified in the Schedule of Assessments (Appendix 1).

Patients who are eligible and consent to receive open-label etrolizumab in Part 1 (OLE) of Study GA28951 are to enroll into Part 1 (OLE) of Study GA28951 directly after the Week 54 visit or the early withdrawal/end of washout visit is completed; they do not enter the 12-week safety follow-up phase of this study.

For patients who are not eligible or who choose not to enroll in Part 1 (OLE) of Study GA28951, the end of study visit, Week 54, or the early withdrawal/end of washout visit is

followed by a 12-week safety follow-up phase consisting of one telephone call 6 weeks after Week 54, and one clinic visit 12 weeks from Week 54, respectively (see Appendix 2). Patients are to then enroll in Part 2 (SM) of Study GA28951 for extended PML follow-up after completion of the 12-week safety follow-up in this study.

4.7.2.3.1 Eligibility for Entry to Open-Label Extension-and Safety-Monitoring Study

Study GA28951 will be conducted under a separate protocol and eligible patients as described below (also see Table 5) will need to be willing and able to provide separate informed consent to enter the study.

Note: Patients who are not eligible or who do not wish to receive open-label etrolizumab in Part 1 (OLE) of Study GA28951 will be requested to enroll in the 92-week extended PML monitoring (Part 2 [SM] of Study GA28951) after completing the 12-week safety follow-up in this study.

The following patients may be eligible to enroll in Part 1 (OLE) of Study GA28951 after the washout period:

- Patients who meet the criteria for disease worsening (see Section 4.6.1 for definition) at any time between Week 10 and Week 54
- All remaining patients at end of Week 54
- Patients who were not receiving corticosteroids at baseline and patients who have completed the steroid taper may be eligible for Part 1 (OLE) of Study GA28951 if they receive oral corticosteroids at a dose greater than 10 mg for 5 days or longer for the treatment of clinical symptoms of either UC or steroid withdrawal during the Maintenance Phase.
- Patients who use IV or topical corticosteroids or topical 5-ASA or who initiate or escalate dose of oral 5 ASA to treat worsening symptoms of UC in the Maintenance Phase
- Patients who require initiation of or an increase in the dose of immunosuppressants during the Maintenance Phase

The following patients are NOT eligible to enroll in Part 1 (OLE) of Study GA28951:

- Patients who discontinue study medication prior to Week 10
- Patients who require rescue medications that are prohibited in conjunction with etrolizumab (see Section 4.4.2.3)
- Patients with severe hypersensitivity reactions (see Section 4.4.2.1), malignancies, specific de novo or reactivated serious viral infections, PML, or other life-threatening infections during the study (see Sections 4.8.1.1, 5.1.1.2, 5.1.1.5, and 5.1.1.1)

A complete list of exclusion criteria for the OLE–SM study can be found in protocol GA28951.

Table 5 Eligibility for Enrollment into Part 1 (OLE) of Study GA28951or Transfer to 12-Week Safety Follow-Up

Time Period	Rationale	May Enroll in Part 1 (OLE) of Study GA28951 after Washout Period	Must Transfer to 12-Week Safety Follow-Up
Day 1 to Week 10	Discontinuation of study treatment	No	Yes (transfer after dosing termination visit)
Week 10 to Week 54	Met criteria for disease worsening (see Section 4.6.1) at any time between Week 10 and Week 54	Yes	Yes (must transfer to SFU if patient does not choose OLE)
Week 10 to Week 54	Initiation or an increase in dose of immunosuppressants	Yes	
Day 1 to Week 54	Use of oral corticosteroids at a dose greater than 10 mg for 5 days or longer for patients who were not receiving corticosteroids at baseline and patients who have completed the steroid taper	Yes	
Day 1 to Week 54	Use of IV or topical corticosteroids or initiated or escalated oral 5 ASA or topical 5-ASA	Yes	
Day 1 to Week 54	Patients requiring rescue medications that are prohibited (see Section 4.4.2.3)	No	Yes (transfer after dosing termination visit)
Day 1 to Week 54	Occurrence of severe hypersensitivity reactions (see Section 4.4.2.1) malignancies, specific de novo or reactivated serious viral infections, PML, or other life-threatening infections during the study (see Sections 4.8.1.1, 5.1.1.2, 5.1.1.4, and 5.1.1.1)	No	
Week 54	End of treatment period (all patients remaining in the study can transfer)	Yes (no additional washout required)	Yes (must transfer to SFU if patient does not choose OLE)

5-ASA = 5-aminosalicylic acid; IV = intravenous; OLE = open-label extension; SFU = safety follow-up; PML = progressive multifocal leukoencephalopathy.

4.7.2.4 Safety Follow-Up Assessments

Safety follow-up will be conducted in this study for a period of 12 weeks for patients not enrolling in Part 1 (OLE) of Study GA28951 (see Table 5 for patients who should enter the 12-week safety follow-up phase within this protocol, Appendix 2). Patients will be assessed at 6-week intervals during this period, one assessment by telephone and one in-person clinic visit. The visits should be scheduled based on the date of the last dose of study drug (e.g., the Week 6 telephone visit should take place 6 weeks after the last dose of study drug). Patients enrolling in Part 1 (OLE) of Study GA28951 will not enter the 12-week safety follow-up period in this study. Adverse events should be followed as outlined in Section 5.4.

Following the 12-week safety monitoring period, patients should enroll in Part 2 (SM) of Study GA28951, where they will be monitored for PML for an additional 92 weeks. Patients enrolling in Part 2 (SM) of Study GA28951 for extended PML monitoring will NOT receive treatment with open-label etrolizumab. During the extended PML follow-up period in Study GA28951, patients will have telephone assessments every 6 months to assess emergence of symptoms and signs of PML. In total, follow-up for the development of any signs or symptoms of PML will be conducted for a period of 2 years after last dose of study drug.

Patients who do not wish to enter safety follow-up or who discontinue from the study during 12-week safety follow-up will be asked to return to the clinic within 30 days (±7 days) after the last scheduled visit for a safety follow-up early termination visit (see Appendix 2).

See Appendix 1 for the schedule of assessments performed at the Week 54 or early withdrawal/end of washout visit.

After the Week 54 or early withdrawal/end of washout visit, adverse events should be followed as outlined in Section 5.5 and Section 5.6.

See Appendix 2 for the schedule of 12-week safety follow-up assessments.

4.7.2.5 Assessments at Unscheduled Visits

An unscheduled visit may occur at any time during the study (i.e., because of relapse of disease or an adverse event). Patients who are seen by the investigator or site staff at a timepoint not required by the protocol because of assessment of potential disease worsening will undergo the following:

- Symptom-directed physical examination
- Vital sign assessment
- Review of e-diary data
- Recording of concomitant medications and procedures
- Collection of adverse events and serious adverse events

- Clinical chemistry hematology and CRP, if indicated
- Stool sample collection, if indicated
- Partial or complete MCS, if indicated
- Flexible sigmoidoscopy, if indicated
- Colonic biopsy to evaluate for CMV, if clinically indicated
- Collection of PK and ATA samples, if indicated

See Appendix 1 for assessments that are to be performed in case of an unscheduled visit.

4.8 PATIENT, STUDY, AND SITE DISCONTINUATION

4.8.1 Patient Discontinuation

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 or non-adherence with background medications

4.8.1.1 Discontinuation from Study Drug

Patients must discontinue study medication (both etrolizumab/etrolizumab dummy and infliximab/infliximab dummy) if they experience any of the following:

- Pregnancy
- Anaphylaxis or other severe hypersensitivity reaction
- Develop colonic mucosal dysplasia
- Malignancy (with the exception of local and resected basal or squamous cell carcinoma of the skin) or cervical Pap test with AIS, HSIL, or CIN of Grade >1
- 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 medication.

  Any patient who develops CMV colitis should discontinue study medication.

  Any patient who develops life-threatening infections during the study should discontinue study medication.
- Any medication for rescue outside defined limits of the protocol (see Section 4.5.2)

Patients who discontinue study drug prematurely for the reasons listed above will be asked to return to the clinic for an early withdrawal visit (see Section 4.7.2.3) followed by the 12-week safety follow-up. Patients should then enroll in Part 2 (SM) of Study GA28951 to undergo safety follow-up assessments for up to 2 years after the last dose of study drug (see Section 4.7.2.4). The primary reason for premature study drug discontinuation must be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced.

4.8.1.2 Withdrawal from Study

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

4.8.2 Study and Site Discontinuation

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.
- Patient enrollment is unsatisfactory.

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:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

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 is not known at this time and will be further characterized during the Etrolizumab Phase III program.

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

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

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 $\alpha4\beta1$, which is inhibited by natalizumab, is a pleiotropic integrin that is believed to facilitate T cell migration into the CNS. Inhibition of integrin $\alpha4\beta1$ 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 $\alpha4\beta7$ integrin and not the $\alpha4\beta1$ integrin, *despite extensive treatment exposure* (Dotan 2017).

Etrolizumab targets cells expressing the $\beta7$ integrin ($\alpha4\beta7$ and $\alpha E\beta7$ cells) and not $\alpha4\beta1$ cells. Despite the lack of theoretical or experimental evidence for a specific role of $\beta7$ 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 studies.

Screening, 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, or rituximab and patients with a history of demyelinating disease or PML. Patients with neurologic disease conditions that may interfere with monitoring for PML, such as clinically significant abnormalities noted at the screening neurologic examination (subjective or objective checklists), should be excluded.

A plasma sample to test for antibodies to JCV will be taken and stored for possible later assessment of how widespread the JCV infection is in the study population. Sample testing for the presence of JCV antibodies is not helpful in predicting risk for PML or for evaluating neurologic symptoms. The sample may be tested if there is a strong belief that this information will be helpful in managing a patient's condition.

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 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) should be administered (see Appendix 5; PML Subjective and Objective Checklists) by a qualified HCP and will be performed at screening and 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 5.2.3 and Appendix 6 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 be resumed only in patients where PML has been ruled out. See Appendix 6 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 5 (Worksheet for the PML Neurologic Examination) and Appendix 6 (Algorithm for the Evaluation of Progressive Multifocal Leukoencephalopathy).

5.1.1.1.2 Other Serious Infections

Background

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

Patient Selection

Patients with congenital or acquired immune deficiency are excluded from the study. Patients with specific and/or recent infections such as CMV colitis, *Clostridium difficile*, and other intestinal pathogens are excluded from the study (see Exclusion Criteria Related to Infection Risk in Section 4.1.2). Patients with a history of recurrent opportunistic infections and/or severe disseminated viral infections or any serious opportunistic infection within the past 6 months are excluded from the study.

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.

Patients with a history of active or latent treated TB, regardless of treatment history, are excluded from the study. Investigators are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

Patients at risk for TB exposure are noted below. Patients who meet these criteria should be evaluated per local practice to exclude latent TB infection.

- Patients who have household contact with a person with active TB
- Patients living in areas with high incidence of TB
- Patients who frequently visit areas with high prevalence of active TB, etc.

Apart from their colitis, patients must be in reasonably good health with no significant uncontrolled comorbidity or clinically significant laboratory results (see Exclusion Criteria Related to General Safety and Exclusion Criteria Related to Laboratory Values [at Screening] in Section 4.1.2).

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 drug 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 therapy requires consultation with the Medical Monitor.

5.1.1.2 Hypersensitivity Reactions

Background

In completed Phase I/II clinical studies 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 with a history of moderate or severe allergic or anaphylactic/anaphylactoid reactions to chimeric, human, or humanized antibodies; fusion proteins; or murine proteins or hypersensitivity to etrolizumab or any of the excipients (L-histidine, L-arginine, succinic acid, polysorbate 20) are excluded from study participation.

Education, Monitoring, and Management

The first four injections should be administered in the clinic. After each of these four injections, the patient must be monitored for 60 minutes. Epinephrine must be readily available at site or 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.

See Appendix 8 (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 studies in patients with UC, 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.

Patient Selection

Patients with significant liver function test abnormalities should be excluded from the etrolizumab clinical studies (see Section 4.1.2).

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 nor evidence for increased incidence of malignancy in completed Phase I/II studies and nonclinical studies to date. Nonetheless, given the elevated risk of malignancy in this patient population a priori, the study includes selection criteria and additional information to minimize any hypothetical risk.

Patient Selection

Patients with a history of cancer, including hematologic malignancy, solid tumors, and carcinoma in situ within 5 years before screening should be excluded from the study with the exception of local basal or squamous cell carcinoma of the skin that has been excised and is considered cured (see Exclusion Criteria Related to General History in Section 4.1.2). A history of chronic myelogenous leukemia, hairy cell leukemia, melanoma, renal cell carcinoma, Kaposi sarcoma, or AIS, HSIL, or CIN of Grade >1 is considered exclusionary irrespective of the length of time before screening.

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 the clinical experience to date, approximately 5% of patients develop ATAs to etrolizumab; however, this has not been correlated with any efficacy or safety sequelae.

Monitoring

To assess for the potential development of immunogenicity, antibody samples will be obtained at baseline, at regular intervals during treatment, and during the Safety Follow-Up Period (see 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 within 4 weeks prior to randomization (Day 1) are excluded from the study. Patients should not receive live attenuated vaccines during the study and for approximately 5 half-lives after final study drug administration.

5.1.2 Risks Associated with Infliximab

Investigators should be aware of the risks associated with infliximab and their management (see Infliximab Summary of Product Characteristics).

5.1.3 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 have rescue 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. See Section 4.7.2.5 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.

Rescue therapy not permitted in conjunction with study drug include treatment with TNF inhibitors, cyclosporine, tacrolimus, sirolimus, MMF, natalizumab, vedolizumab, rituximab, other lymphocyte-depleting agents (except AZA and 6-MP), anakinra, abatacept, or other biological or investigational therapeutics 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 study drug or open-label treatment and are to enter into safety follow-up within this study, followed by enrollment into the safety monitoring portion (Part 2 [SM]) of Study GA28951. If a patient meets criteria for disease worsening (see Section 4.6.1) or requires the use of permitted rescue therapy, they may be eligible to enroll in Part 1 (OLE) of Study GA28951) after a period of infliximab washout (see Table 3). Patients who do not enter the Part 1 (OLE) of Study GA28951 will be requested to continue in safety follow-up followed by enrollment into the safety monitoring portion (Part 2 [SM]) of Study GA28951.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

According to the International Council for Harmonisation (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) (see Sections 5.3.5.8 and 5.3.5.9.
- 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, concomitant treatment, or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsy sample collections)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- 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 5.3.5.10)

- 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 (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study 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 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- 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 8)

  Neurologic 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 6 and Section 5.1.1.1.1)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4, 5.5, and 5.6. The investigator is also responsible for reporting medical device complaints (see).

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until the patient completes his or her last study visit. After this period, for patients who enter Study GA28951, adverse event reporting should follow requirements of Study GA28951.

If the patient does not enter Study GA28951, the Sponsor should be notified if the investigator becomes aware of any post-study serious adverse events that are believed to be related to prior study drug treatment. 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 (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4. 0) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 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 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (also see Table 7):

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

Table 7 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria 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 2 days after first dose of study drug).

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 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 following study drug injection should be separately captured as individual signs (e.g., erythema at injection site) and symptoms (e.g., pain 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.

5.3.5.2 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. 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 gastrointestinal 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.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should be recorded only once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be

recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from “non-serious” to “serious,” providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.4 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 $\times$ 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 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 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 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 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 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

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

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

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

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

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

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

5.3.5.9 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").

5.3.5.10 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 5.2.2), 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

5.3.5.11 Adverse Events Associated with an Overdose or Error in Study 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 an adverse event unless it results in untoward medical effects.

Any study drug overdose or error in administration of study drug (e.g., dosing outside of the allowed window or 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 or 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 5.4.2).

5.3.5.12 Electronic Patient-Reported Outcome Data

Adverse event reports will not be derived from electronic Patient-Reported Outcome (ePRO) data *by the Sponsor, and safety analyses will not be performed using ePRO data. Sites are not expected to review the ePRO data for adverse events.*

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 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.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Primary Contact

Medical Monitor:	[redacted], M.B., Ch.B.
Primary:	+1 973 659 6677
Secondary:	+1 570 819 8565

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

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

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

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the patient completes his or her last study visit. 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 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.

Instructions for reporting serious adverse events that occur after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 24 weeks after the final 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.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 24 weeks after the final 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.

5.4.3.3 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 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.4.4 Reporting Requirements for Medical Device Complaints

See Section 4.4.6 for reporting requirements for medical devices.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

5.5.2 Sponsor Follow-Up

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

5.6 POST-STUDY ADVERSE EVENTS

For patients who enter Study GA28951, adverse event reporting should follow the requirements for Study GA28951.

Post-study, if the patient does not enter Study GA28951, the Sponsor should be notified if the investigator becomes aware of any serious adverse event occurring after the end of the adverse event reporting period (defined as the last study visit [see Section 5.3.1]) if the event is believed to be related to prior study drug treatment. In addition, the Sponsor should also be notified if the investigator becomes aware of any post-study events of confirmed or suspected PML, regardless of relationship to study drug, for up to 2 years after the patient's last dose of study drug.

The investigator should report these events directly to Roche or its designee either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax numbers or email address provided to investigators.

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events for etrolizumab using the following reference document:

- Etrolizumab Investigator's Brochure

  Within the Investigator's Brochure, the reference safety information is provided in Section 6 (Identified Risks and Adverse Drug Reactions [Reference Safety Information]).

To determine reporting requirements for single adverse event cases for infliximab, the Sponsor will assess the expectedness of these events using the reference safety information in the E.U. SmPC for infliximab.

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 study 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 FDA. For the FDA, SUSARs will be submitted as IND Safety Reports in line with the FDA guidance "Safety Reporting Requirements for INDs and BA/BE Studies" dated December 2012.

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The analysis of data from the 54-week treatment period will be performed when all data from this period are in the database and data have been cleaned and verified.

Sponsor personnel will be unblinded to treatment assignment to perform the primary Week 54 analysis. Patients and study site personnel will remain blinded to individual treatment assignment until after the study is completed (after all patients have either completed the safety follow-up periods or discontinued early from the study) and the database is locked.

Detailed specifications of the statistical methods will be described in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

Approximately 390 patients will be randomized in a 1:1 ratio to etrolizumab + infliximab dummy or infliximab + etrolizumab dummy. The sample size of 195 patients per group provides $approximately$ 80% power to detect a clinically meaningful difference of 12% (18% vs 30%) between the two groups for the primary endpoint, using a two-sided χ^2 test at a significance level of 0.05.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients randomized will be tabulated by study site, and treatment arm. Patient disposition (the number of patients randomized, treated, and completing each study period) will be tabulated by treatment arm. Reasons for premature study drug discontinuation or withdrawal from study, any eligibility criteria deviations and other major protocol deviations will be summarized by treatment arm.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics such as age, sex, race, region, use of corticosteroids and immunosuppressants at baseline, duration of disease and baseline MCS and its subscores will be summarized for all randomized patients by treatment group by use of descriptive statistics. Exposure to study drug (number of study treatments and duration of treatment) and comparator (infliximab/infliximab dummy) will be summarized by treatment arm.

Baseline is defined as the last assessment prior to the initiation of study treatment.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all randomized patients who received at least one dose of study drug with patients grouped according to the treatment assigned at randomization (Day 1) (intent-to-treat [ITT] population). A per-protocol population will be defined in the SAP for the purpose of testing for non-inferiority in induction of clinical remission at Week 10.

To manage the overall type I error, the testing of hypotheses will be performed sequentially. The primary endpoint will be tested first at an overall two-sided significance level of $\alpha = 0.05$. The testing hierarchy for the secondary endpoints will be described in the SAP.

Unless otherwise noted, analyses of efficacy outcome measures will be stratified by the stratification factors used at randomization (Day 1): baseline corticosteroids use (yes/no), baseline immunosuppressants use (yes/no), and baseline disease severity as measured during screening (MCS ≤ 9 vs. MCS ≥ 10).

Patients who are non-evaluable for efficacy at a specific timepoint (e.g., due to missing data or early transfer to the Part 1 (OLE) of Study GA28951) will be considered non-responders for all response/remission type endpoints. In addition, initiation of an agent not allowed in combination with etrolizumab or infliximab, an immunosuppressant, oral or topical 5-ASA (up to Week 10), or corticosteroid, or increase in dose over baseline levels for treatment of worsening disease symptoms as defined in Section 3.1.1.1 will lead to non-responder classification thereafter.

For continuous outcomes, scores after the first use of rescue medication will be imputed using the worst post-baseline score from the following assessments: the last score available prior to the start date of first rescue medication and all scores available after the start date of rescue medication use.

In addition to the analyses described in Section 6.4.1 and Section 6.4.2, the following analyses will be performed for the primary efficacy endpoint and key secondary efficacy endpoints. Details of these analyses will be described in the SAP:

- Sensitivity analyses to evaluate the robustness of results to the primary analysis methods (e.g., handling of dropouts)
- Subgroup analyses to evaluate the consistency of results across prespecified subgroups (e.g., based on age, sex, race/ethnicity, baseline UC medications, baseline CS dose)

6.4.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the proportion of patients achieving both clinical response at Week 10 and clinical remission at Week 54.

The primary endpoint will be compared between the etrolizumab and infliximab arms by using the Cochran-Mantel-Haenszel test statistic, stratified by the factors used at randomization (Day 1). The absolute difference in remission rates and 95% CI for the point estimate will be provided.

Further details will be included in the SAP.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study are as follows:

- Proportion of patients achieving clinical remission at Week 10
- Proportion of patients achieving clinical remission at Week 54
- Proportion of patients achieving clinical remission at both Week 10 and Week 54
- *Proportion of patients achieving clinical remission at Week 54 among patients with a clinical response at Week 10*
- Proportion of patients achieving improvement in endoscopic appearance of the mucosa at Week 10
- Proportion of patients achieving improvement in endoscopic appearance of the mucosa at Week 54
- Proportion of patients achieving improvement in endoscopic appearance of the mucosa at both Week 10 and Week 54
- Proportion of patients in endoscopic remission at Week 54
- Proportion of patients achieving clinical response at Week 10
- Proportion of patients achieving clinical response at both Week 10 and Week 54
- Proportion of patients in corticosteroid-free (off corticosteroid for at least 24 weeks prior to Week 54) clinical remission at Week 54 in patients who were receiving corticosteroids at baseline
- Change from baseline in patients' health-related QOL at Weeks 10, 30, and 54 as assessed by the overall score of the IBDQ

Induction of remission will be evaluated at Week 10. Remission is defined as an MCS ≤ 2, with no individual score > 1 and a rectal bleeding subscore of 0.

For secondary responder type endpoints, superiority will be assessed in the same fashion as for the primary endpoint.

A 95% two-sided CI will be constructed for the difference in clinical remission rates at Week 10 between the two groups (etrolizumab minus infliximab). If the lower limit of the CI is $\geq 12.5\%$, it will be inferred that etrolizumab is non-inferior to infliximab for induction of clinical remission at Week 10. If the lower limit of the CI is $> 0\%$, it will be inferred that etrolizumab is superior to infliximab for induction of clinical remission at Week 10.

Continuous endpoints will be analyzed using an analysis of covariance (ANCOVA) model, adjusting for baseline score, and the stratification factors used at randomization (Day 1).

Further details will be provided in the SAP.

6.4.3 Exploratory Efficacy Endpoints

- Proportion of patients achieving remission at Week 10
- Proportion of patients achieving remission at Week 54
- Proportion of patients achieving remission at both Week 10 and Week 54
- Change in health utilities, as assessed by EQ-5D, from baseline to weeks 10, 30, and 54
- Frequency and duration of hospitalizations from baseline to Week 54

6.5 SAFETY ANALYSES

The safety analyses will include all randomized patients who received at least one dose of study drug, with patients grouped according to the treatment actually received.

6.5.1 Laboratory Tests

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

The number and percentage of patients with positive serum antibodies to etrolizumab, or, if required, infliximab at baseline and during the study will be tabulated by treatment arm.

6.5.2 Adverse Events

Verbatim descriptions of treatment-emergent adverse events will be coded, and their incidence will be summarized by treatment arm, 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 study drug. 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 using the anaphylactic reaction Sampson's criteria (see Appendix 8).

- Serious infections

  The frequency of serious infections, in particular GI infections, will be summarized for each treatment arm.

- Opportunistic infections

  The occurrence of opportunistic infections will be summarized for each treatment arm.

- Malignancies

  Events that occur in the Neoplasms, Benign, Malignant, and Unspecified (Including Cysts and Polyps) System Organ Class will also be summarized for each treatment arm.

- Injection-site reactions

  The frequency of injection-site reactions will be summarized for each treatment arm.

6.6 PHARMACOKINETIC, PHARMACODYNAMIC, AND BIOMARKER ANALYSES

For PK assessment (PK substudy on approximately 200 etrolizumab-treated patients), group average serum–etrolizumab concentration versus time data will be tabulated and plotted. The serum PKs of etrolizumab will be summarized at Week 12 and at Weeks 10, 30, and 54. Estimates for these parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum).

Additional PK analyses may be conducted as appropriate.

Biomarker analyses will include examination of the relationship between baseline biomarkers and response to treatment *at Week 10 and Week 54*, and of changes *relative to baseline* in exploratory biomarkers *during and at end of* treatment. Results will be summarized descriptively.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

Sponsor, contract research organization (CRO), and Data Management vendor will be responsible for the data management of this study, including quality checking of the data. Sites will be responsible for data entry into an 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 the Help Text in 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 ePRO vendor. The electronic devices are designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 Code of Federal Regulations, Part 11). The data will be transmitted to a centralized database at the ePRO vendor. The data from the ePRO 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 devices are 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 SDV 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, PRO questionnaires, 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, ECGs, MRIs, 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 SDV, 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 (including PRO) data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the

ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms 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 Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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).

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 include an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This study is sponsored by F. Hoffmann–La Roche Ltd. Approximately 200 international study centers will participate in this study to enroll approximately 390 patients.

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

Centralized facilities (vendors) will be used to collect endoscopy reading and interpretation; however, the investigator or a designee will also read the endoscopy as part of the MCS evaluation.

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 and urine pregnancy tests will be conducted by the patient at home if appropriate.

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

An iDMC will be established to perform regular review of the safety data to ensure the ongoing safety of participating patients. Its composition and a description of its responsibilities will be provided in an iDMC charter.

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).

10. REFERENCES

Bradley GM, Oliva-Hemker M. Infliximab for the treatment of pediatric ulcerative colitis. Expert Rev Gastroenterol Hepatol 2012;6:659–65.

Cepek KL, Parker CM, Madara JL, et al. Integrin $\alpha^E\beta_7$ mediates adhesion of T lymphocytes to epithelial cells. J Immunol 1993;150:3459–70.

Chang JT, Lichtenstein GR. Drug insight: antagonists of tumor-necrosis factor-α in the treatment of inflammatory bowel disease. Nat Clin Pract Gastroenterol Hepatology 2006;3:220.

Chebli LA, Chaves LD, Pimentel FF, et al. Azathioprine maintains long-term steroid-free remission through 3 years in patients with steroid-dependent ulcerative colitis. Inflamm Bowel Dis 2010;4:613–9.

Dotan, I. Early use of gut-selective therapy in Crohn's disease for long-term remission. Presented at Takeda-organized symposium during the 12th Congress of European Crohn's and Colitis Organization, 17 February 2017 (unpublished).

Faubion WA Jr, Loftus EV Jr, Harmsen WS, et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology 2001;121:255–60.

Feagan BG, Greenberg GR, Wild G, et al. Treatment of active Crohn's disease with MLN0002, a humanized antibody to the alpha4beta7 integrin. Clin Gastroenterol Hepatol 2008;6:1370–7.

Feagan BG, Greenberg GR, Wild G, et al. Treatment of ulcerative colitis with a humanized antibody to the α4β7 integrin. N Engl J Med 2005;352:2499–507.

Feagan BG, Rutgeerts PG, Sand BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013;369:699–710.

Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology 1989;96:804–10.

Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541–49.

Holzmann B, McIntyre BW, Weissman IL. Identification of a murine Peyer's patch–specific lymphocyte homing receptor as an integrin molecule with an α-chain homologous to human VLA-4-α. Cell 1989;56:37–46.

Hu M, Crowe DT, Weissman IL, et al. Cloning and expression of mouse integrin βp(β7): a functional role in Peyer's patch–specific lymphocyte homing. Proc Natl Acad Sci USA 1992;89:8254–8.

Irvine EJ. Development and subsequent refinement of the inflammatory bowel disease questionnaire: a quality-of-life instrument for adult patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 1999;28:S23–7.

Khan N, Abbas AM, Moehlen M, et al. Methotrexate in ulcerative colitis: a nationwide retrospective cohort from the Veterans Affairs Health Care System. Inflamm Bowel Dis. 2013; 19:7.

Laharie D, Bourreille A, Branche J, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet 2012; 380:1909–15.

Lobel EZ, Korelitz BI, Xuereb MA, et al. A search for the optimal duration of treatment with 6-mercaptopurine for ulcerative colitis. Am J Gastroenterol 2004; 3:462–5.

Mañosa M, García V, Castro L, et al. Methotrexate in ulcerative colitis: a Spanish multicentric study on clinical use and efficacy. J Crohns Colitis 2011;5:397–40.

Molodecky NA, Soon IS,Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142:46–54.

Rabin R, deCharro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337–43.

Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462–76.

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.

Sandborn WJ, Colombel JF, D'Haens G, et al. One-year maintenance outcomes among patients with moderately-to-severely active ulcerative colitis who responded to induction therapy with adalimumab: subgroup analyses from ULTRA 2. Aliment Pharmacol Ther 2013;37:204–13.

Sandborn WJ, Colombel JF, Enns R, et al. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med 2005;353:1912–25.

Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2017;376:1723–36.

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.

Tan IL, McArthur JC, Clifford DB, et al. Immune reconstitution inflammatory syndrome in natalizumab-associated PML. Neurology 2011;77:1061–77.

Appendix 1
Schedule of Assessments

Assessment	Clinic Visit Schedule (Etrolizumab/Etrolizumab Dummy Administration in Clinic)	Weeks (± 3 days) Clinic Visit/Telephone Contact Schedule (Etrolizumab/Etrolizumab Dummy Administration at Home)																														
	SD −35 to −1	0 [c]	2	4	6	8	10	12	14	16	18 [d]	20	22	24	26 [d]	28	30	32	34 [d]	36	38	40	42 [d]	46	48	50 [d]	52	54	UV/ D-OLE [b]	EW/ WO
Informed consent	x																														
Review eligibility criteria	x [e]	x																													
Demographic data	x																														
Pregnancy test [f]	x	x		x		x		x																							x
Vital signs (BP and pulse)	x	x		x		x			x	x		x	x	x		x	x	x		x	x	x		x	x		x	x			x
ECG	x																											x			x
Chest X-ray [g]	x																														
Height		x																													
Weight		x																													
Medical history	x																														
Physical examination [h]	x						x						x				x				x			x				x	x [b]	x
PML neurologic examination [i]	x			x			x						x								x							x	x [b]	x
Hematology	x	x					x						x								x							x	x [b]	x [j]

Appendix 1
Schedule of Assessments (cont.)

Assessment	Clinic Visit Schedule (Etrolizumab/Etrolizumab Dummy Administration in Clinic)	Weeks (± 3 days) Clinic Visit/Telephone Contact Schedule (Etrolizumab/Etrolizumab Dummy Administration at Home)																													
	SD −35 to −1	0 [c]	2	4	6	8	10	12	14	16	18 [d]	20	22	24	26 [d]	28	30	32	34 [d]	36	38	40	42 [d]	46	48	50 [d]	52	54	UV/ D-OLE [b]	EW/ WO
Chemistry	x	x					x						x								x							x	x [b]	x [j]
Urinalysis	x	x																											x [b]	
TB screen [k]	x																													
HIV test	x																													
Hepatitis B and C serology [l]	x																													
Hepatitis B DNA [m]	x						x						x								x							x		
Hepatitis C RNA (Amplicor) [n]	x																													
PK sampling (serum) [o, p]		x	x				x	x									x											x	x [b]	x [j]
Anti-therapeutic ant body sample (serum) [o, p, q]		x		x			x	x [o]									x [o]											x [r]	x [b]	x [j r]
Plasma sample (storage for JCV antibody testing) [s]	x																													

Appendix 1
Schedule of Assessments (cont.)

Assessment	Clinic Visit Schedule (Etrolizumab/Etrolizumab Dummy Administration in Clinic)	Weeks (± 3 days) Clinic Visit/Telephone Contact Schedule (Etrolizumab/Etrolizumab Dummy Administration at Home)																													UV/ D-OLE [b]	EW/ WO
	SD −35 to −1	0 [c]	2	4	6	8	10	12	14	16	18 [d]	20	22	24	26 [d]	28	30	32	34 [d]	36	38	40	42 [d]	46	48	50 [d]	52	54		
MCS (includes endoscopy) [t, u]	x [v]						x																					x	x [b]	x [j, gg]
pMCS (excludes endoscopy) [u, w]		x [v]		x		x		x					x				x				x			x					x [b]	x [j]
Stool sample collection	x [x]	x [y]					x [y]										x [y]											x [y]	x [b]	x [y]
Colonic biopsy (CMV if required)	x [z]																												x [b]	
Colonic biopsy (histopathological confirmation of UC if required)	x [aa]																													
Colonic biopsies (formalin)	x [bb]						x [cc]																					x [cc]	x [b, cc]	x [j, cc, gg]
Colonic biopsies (for qPCR)	x [bb]						x [cc]																					x [cc]	x [b, cc]	x [j, cc, gg]
Serum sample (CRP) [p]		x					x																					x	x [b]	x [j]
Serum sample (future exploratory PD) [o, p]		x	x				x	x									x											x		x

Appendix 1
Schedule of Assessments (cont.)

Assessment	Clinic Visit Schedule (Etrolizumab/Etrolizumab Dummy Administration in Clinic)	Weeks (± 3 days) Clinic Visit/Telephone Contact Schedule (Etrolizumab/Etrolizumab Dummy Administration at Home)																												UV/ D-OLE [b]	EW/ WO
	SD −35 to −1	0 [c]	2	4	6	8	10	12	14	16	18 [d]	20	22	24	26 [d]	28	30	32	34 [d]	36	38	40	42 [d]	46	48	50 [d]	52	54		
Blood sample (RNA Paxgene) [o, p, dd]		x	x				x										x											x		x
Whole blood (EDTA) optional [p]		x																												
IBDQ [ee]		x					x										x											x		
EQ-5D [ee]		x					x										x											x		
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Infliximab/ infliximab dummy administration		x	x		x				x				x				x				x			x						
Etrolizumab/ etrolizumab dummy administration		x		x		x		x		x		x		x		x		x		x		x			x		x			

Appendix 1
Schedule of Assessments (cont.)

Ab = antibody; ATA = anti-therapeutic antibody; BP = blood pressure; CMV = cytomegalovirus; CRP = C-reactive protein; D-OLE = decision to switch to OLE; ECG = electrocardiogram; EQ-5D = EuroQoL Five-Dimension Questionnaire; eCRF = electronic case report form; EW = early withdrawal; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IBDQ = Inflammatory Bowel Disease Questionnaire; JCV = John Cunningham virus; MCS = Mayo Clinic Score; PD = pharmacodynamics; PK = pharmacokinetic; pMCS = partial Mayo Clinic Score; PML = progressive multifocal leukoencephalopathy; qPCR = quantitative polymerase chain reaction; SD = screening day; TB = tuberculosis; UC = ulcerative colitis; UV = unscheduled visit; WO = washout.

Notes:

- Study assessments and blood draws are to be conducted prior to study drug administration
- All colonic biopsy samples will be taken during flexible sigmoidoscopy/colonoscopy procedure.
- Etrolizumab administration at home for eligible patients on Weeks: 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (negative urine pregnancy test, preferably performed in home setting, required prior to administration)

[a] All assessments must be performed after obtaining informed consent. Endoscopy is to be performed 4–16 days prior to randomization (Day 1). The total screening period is 35 days. Under no circumstances will either window be extended.

[b] Unscheduled visit (including decision to switch to OLE) represents a visit that is not as per schedule of assessment and is required for an adverse event or for potential disease worsening 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 of PML; for disease worsening, infectious etiologies may be investigated if clinically indicated; and confirmation of disease worsening is performed by the Mayo Clinic Score assessment). Assessments corresponding to items noted in this column should be recorded on the eCRF. Refer to Table 3 for details regarding washout and timing of enrollment in Part 1 (OLE) of Study GA28951.

[c] Day 1 of Week 0.

[d] Telephone contact for patients performing home administration: patients requiring in-clinic drug administration throughout the study will have their study assessments conducted in clinic or via telephone call after their clinic visit at the sites' discretion.

[e] Perform prior to first administration of study drug.

[f] Serum test at screening for all female patients except those who are more than 1 year postmenopausal or have had a hysterectomy. Urine test at other visits; if urine test is positive, perform a confirmatory serum test. Pregnancy test will be carried out at home once patient starts etrolizumab administration at home. Patient is to report the pregnancy test via e-diary. Patients must be instructed at screening and reminded throughout the study that in case of positive pregnancy test they must stop self-administration of study drug and call the site immediately. Do not administer etrolizumab unless the serum pregnancy test result is negative. After Week 12, pregnancy tests to be performed prior to administration and preferably in home setting at Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52.

[g] Not required if normal chest X–ray result within 3 months prior to screening.

Appendix 1
Schedule of Assessments (cont.)

[h] Full physical examination required at screening; symptom-driven physical examination at all other timepoints indicated.

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

[j] Not required if unscheduled visit leads to withdrawal or decision to switch to OLE (Part 1) and assessment was previously conducted at unscheduled visit.

[k] The following tests are acceptable screening assays for latent TB in this study: purified protein derivative (a tuberculin skin test reaction aka Mantoux test), INF-γ based test (e.g., QuantiFERON®-TB Gold).

[l] Patients must undergo screening for HBV and HCV. This includes testing for HBsAG (HBV surface antigen), anti-HBc total (HBV core antibody total), and hepatitis C antibody.

[m] Enrolled patients who are hepatitis B core antibody positive should have hepatitis B DNA measured at these timepoints.

[n] Measurement of HCV RNA with use of the Amplicor assay is required only when the patient has a known history of HCV antibody positivity with past documentation of undetectable HCV RNA, either with or without history of anti-viral treatment. Patients with newly diagnosed HCV antibody positivity are not eligible for this study, and therefore do not require measurement of HCV RNA.

[o] Samples to be collected from a subset of patients (approximately 400 at designated sites) for PK (all scheduled timepoints), ATA (indicated times) and exploratory PD assessment (all scheduled timepoints). ATA samples at baseline Week 0, Week 10, and Week 54 are to be collected from all patients and all ATA samples may be used for exploratory PD and/or PK assessment.

[p] Samples are to be collected prior to dose administration (blood, serum, colonic biopsies).

[q] If serum sickness or a clinically significant allergic drug reaction is suspected, Sponsor should be notified and serum for the analysis of study drug level 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.

[r] Collection of sample for ATA is required at final or early withdrawal visit, unless it coincides with first visit in Part 1 of Study GA28951 (where a sample for ATA must be collected).

[s] A blood sample to test for antibodies to JCV will be taken and stored for possible later assessment of how widespread the JCV infection is in the study population. Sample testing for the presence of JCV antibodies is not helpful in predicting risk for PML or for evaluating neurologic symptoms. The sample may be tested if there is a strong belief that this information will be helpful in managing a patient's condition.

[t] Endoscopy + rectal bleeding assessment + stool frequency assessment + Physician's Global Assessment. Patients who have not undergone full colonoscopy with documented results within one year prior to screening should undergo colonoscopy in lieu or sigmoidoscopy at the screening visit to allow for screening for cancer/dysplasia (yes/no). Rectal bleeding and stool frequency to be collected daily on e-diary.

[u] During screening, patients must be trained on the use of the e-diary. Patients are to complete the e-diary on a daily basis for the stool frequency and rectal bleeding score (for MCS/pMCS) from first screening visit.

[v] Partial MCS during screening is defined as the MCS score excluding the endoscopy score. Screening endoscopy (for the MCS) is to be performed between 4–16 days prior to randomization (Day 1) (i.e., Day –16 to Day –4. For baseline measurements, the Physician's Global Assessment will be obtained only once, on Day 1 (prior to randomization [Day 1)]), and the Physician's Global Assessment score will be used to calculate both the baseline (screening) MCS and the baseline (Day 1) pMCS.

[w] Rectal bleeding assessment + stool frequency assessment + Physician's Global Assessment. Rectal bleeding and stool frequency to be collected daily on e-diary.

[x] For culture and sensitivity testing; ova, parasites, and *Clostridium difficile* toxin testing.

[y] Sample analyses may include, but are not limited to, analyses of fecal calprotectin, and other exploratory PD biomarkers (such as analyses of the microbiota and bacterial cultures).

[z] IF REQUIRED: If there is suspicion for clinically significant CMV colitis, one biopsy sample should be obtained from the base of the ulcer to evaluate for histological presence of CMV. Analysis should be performed locally if possible, or can be sent to a central laboratory if necessary. Result must be negative for CMV prior to dosing on Day 1.

[aa] IF REQUIRED: If patient does not have previously documented histopathologic confirmation of UC as defined in the inclusion criteria, one biopsy sample can be obtained from the base of the ulcer and read locally for histopathologic confirmation of UC.

[bb] In addition to the optional biopsy noted in footnote "z" and "aa" above, five pairs (10 biopsy samples) will be obtained at screening (all taken from the most inflamed area of colon within 20–40 cm of anal verge [sigmoid]). These five biopsy pairs will be sent to the central laboratory for further storage or distribution. Two pairs will be placed in stabilization buffer (such as RNAlater or a similar buffer) and stored at –80°C (one pair for diagnostic qPCR and one pair for PD biomarkers qPCR). In the United Kingdom (U.K.) sites only, one of the latter pair of biopsies (two samples) will be placed in storage solution and shipped at 4°C to the U.K. laboratory. The other three pairs will be placed in formalin and then paraffin embedded; these biopsy samples will be used for exploratory PD biomarkers and/or diagnostic biomarkers. Original biopsy location and endoscopic depth should be clearly indicated.

[cc] A total of four pairs (8 biopsy samples) will be obtained from all patients (all taken from the most inflamed area of colon within 20–40 cm of anal verge [sigmoid]). All will be sent to the central laboratory for further storage or distribution. Two pairs will be placed in a stabilization buffer (such as RNAlater or a similar buffer) and stored at –80°C for exploratory PD biomarker and/or diagnostic biomarker qPCR.

In the U.K. sites only, one of the latter pair of biopsies (two samples) will be placed in storage solution and shipped at 4°C to the U.K. laboratory. The other two pairs will be placed in formalin and then paraffin; these biopsy samples will be used for exploratory PD biomarkers and/or diagnostic biomarkers. Original biopsy location and endoscopic depth should be clearly indicated.

[dd] Paxgene blood RNA samples must be collected after all other blood and serum samples.

[ee] With the exception of Week 0, the IBDQ and EQ-5D will be completed in-clinic by the patient before any other non-PRO assessments and before the patient receives any disease-status information or study drug during that visit.

[ff] Where indicated, patients must be instructed to administer study drug at home within 3 days (maximum) after clinic visit.

[gg] *For patients exiting the treatment period early for any reason, an endoscopy to document disease activity may be performed at the discretion of the investigator.*

Appendix 2
12-Week Safety Follow-Up

Assessment	Week (±3 days)		
	6 [a]	12/Early Termination [b]	Unscheduled Visit [c]
ECG		x	
PML neurologic examination [d]		x	
PD sampling (serum) [e]		x	
PK sampling (serum) [e]		x	
Anti-therapeutic antibody sample (serum) [f]		x	
Medication changes	x	x	x
Adverse events	x	x	x

ATA = anti-therapeutic antibody; ECG = electrocardiogram; PK = pharmacokinetic; PD = pharmacodynamic; PML = progressive multifocal leukoencephalopathy.

[a] Week 6 study assessments are to be made by telephone call and not by clinic visit.

[b] Denotes early termination visit from safety follow-up period.

[c] Unscheduled visit for safety monitoring.

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

[e] Samples taken from the 400-patient subset at designated sites.

[f] Samples taken from all patients and whenever serum sickness is suspected. Samples may be used for PK and/or exploratory PD assessments.

Appendix 3
Childbearing Potential, Pregnancy Testing, and Contraception

All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening and a urine pregnancy test prior to administration of study drug at subsequent visits. If a urine pregnancy test result is positive, study drug will not be administered until pregnancy is ruled out. The result must be confirmed by a serum pregnancy test (conducted by the central laboratory). Refer to Section 5.4.3 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 contraceptive pill
- Contraceptive transdermal patch
- Intrauterine device
- Implants for contraception
- Injections for contraception (with prolonged release)
- Hormonal vaginal device
- Sterilization, surgical tubal ligation
- Sole sexual partner consisting of surgically sterilized male partner with appropriate postsurgical verification of the absence of spermatozoa in the ejaculate

Appendix 3
Childbearing Potential, Pregnancy Testing, and Contraception (cont.)

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

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

For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

> With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 24 weeks after the last dose of study drug. Men must refrain from donating sperm during this same period.

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

Appendix 4
Mayo Clinic Score Measurement

Mayo Clinic Score 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

1. 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

2. 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

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

4. 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 4
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 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. This value will remain stable throughout the 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 is to be ignored (bowel preparation and endoscopy procedure days are to be loaded into the e-diary by the patient and excluded from the MCS calculation).

1. Stool frequency

- Stool frequency is to be recorded daily from start of screening to the end of the study in the e-diary
- The stool frequency is to be compared with the normal frequency and 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 DOES NOT COUNT as stool.
- The baseline stool frequency value will be taken from patient e-diary recordings that are entered between Day –22 (inclusive) and bowel preparation for the screening endoscopy and will be calculated as the average (rounded to the nearest integer) from the three most recent stool frequency scores that were entered just prior to the day of bowel preparation. However, up to three post-endoscopy scores, starting with the score recorded 2 days after the endoscopy, may be used to calculate baseline stool frequency, but ONLY when fewer than three scores are available between Day –22 and bowel preparation. The days selected for this calculation are intended to prevent the use of stool frequency recordings during the screening period that are impacted by bowel preparation and endoscopy, including the day immediately following the endoscopy.

Appendix 4
Mayo Clinic Score Measurement (cont.)

- *For patients undergoing re-screening who meet the criteria to waive the endoscopy (see Section 4.7.2.1.2), the stool frequency subscore will be derived from the 3 consecutive days prior to the new enrollment day (i.e., Days -1, -2, and -3). Any missing day or days will be supplemented with the immediate next day or days recorded up to 22 days prior to the new enrollment day (e.g., if Day -2 is missing, Days -1, -3, and -4 will be used).*
- The post-baseline stool frequency value for endpoint assessment will be calculated as the average (rounded to the nearest integer) of the three most recent stool frequency scores that were entered in the e-diary within the 7 days prior to the clinic visit (and prior to the days devoted to bowel preparation and endoscopy.

2. Rectal bleeding

- Rectal bleeding is to be recorded daily from screening to the end of the study in the e-diary.
- The rectal bleeding score is to be categorized from 0–3 according to the definition given in 2 above.
- Patients are to be instructed to ignore any blood that is caused by menstruation or hemorrhoids.
- The baseline value for the rectal bleeding score will be taken from patient e-diary recordings that are entered between Day –22 (inclusive) and bowel preparation for the screening endoscopy and will be determined by the worst recording from the three most recent scores that were entered just prior to the day of bowel preparation. However, up to three post-endoscopy scores, starting with the score recorded 2 days after the endoscopy, may be used to calculate baseline rectal bleeding, but ONLY when fewer than three scores are available between Day –22 and bowel preparation (see Figure 1 below). The days selected for this calculation are intended to prevent the use of rectal bleeding recordings during the screening period that are impacted by bowel preparation and endoscopy, including the day immediately following the endoscopy.
- *For patients undergoing re-screening who meet the criteria to waive the endoscopy (see Section 4.7.2.1.2),, the rectal bleeding subscore will be derived from the 3 consecutive days prior to the new enrollment day (i.e., Days -1, -2, and -3). Any missing day or days will be supplemented with the immediate next day or days recorded up to 22 days prior to the new enrollment day (e.g., if Day -2 is missing, Days -1, -3, and -4 will be used).*
- The post-baseline 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 within the 7 days prior to the clinic visit and prior to the days devoted to bowel preparation and endoscopy.

Appendix 4
Mayo Clinic Score Measurement (cont.)

3. Endoscopy Subscore

This score is provided by the endoscopy reading vendor as a subscore of 0 to 3.

- Findings on endoscopy will be documented by photographic evidence (central reading of endoscopy videos)
- The score will be based upon the worst affected segment (if mucosal appearance varies) *for study conduct,* except at post-baseline time points, when the sigmoid colon MCS endoscopic subscore will be used if the baseline sigmoid colon MCS endoscopic subscore is 2–3.

  Note: The time window for performing endoscopy during the screening is 4–16 days prior to randomization (Day 1) (i.e., Day –16 to Day –4).

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 examination 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.

CALCULATION OF THE MAYO CLINIC SCORE

Timepoints for MCS assessments can be found in the protocol Schedule of Assessments.

1. Eligibility for enrollment

Moderately to severely active ulcerative colitis as determined by a Mayo Clinic Score of 6–12 with an endoscopic subscore ≥ 2, a rectal bleeding subscore ≥ 1, and a stool frequency subscore ≥ 1

Appendix 4
Mayo Clinic Score Measurement (cont.)

2. Achievement of clinical response at Week 10

MCS with ≥3-point decrease and 30% reduction from baseline as well as ≥1-point decrease in rectal bleeding subscore or an absolute score of 0 or 1

3. Identification of Disease Worsening

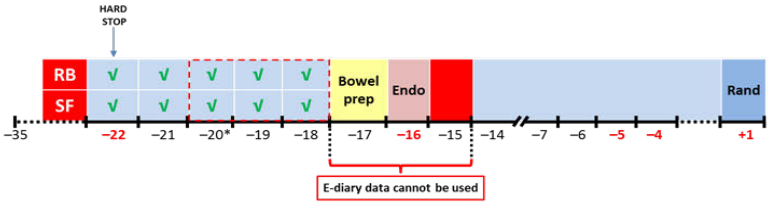
Disease worsening is defined as an increase in pMCS ≥3 points compared to Week 10 AND absolute pMCS of ≥5 AND an endoscopy subscore of ≥2

Appendix 4
Mayo Clinic Score Measurement (cont.)

Figure 1 Derivation of Stool Frequency and Rectal Bleeding Subscores at Screening

Scenario 1: Sufficient e-Diary Data Available prior to Endoscopy at Day –16

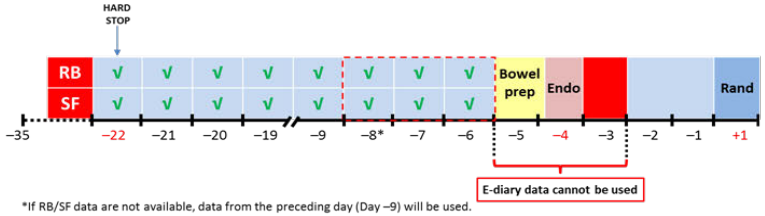
The e-diary data from the 3 consecutive days immediately preceding the bowel preparation day (Day –17 in this scenario) are used to derive RB and SF data for MCS calculation (Day –20 to Day –18, highlighted with red dashed lines in the figure). If e-diary data from these days are missing, RB/SF data from the preceding days (Day –21 or Day –22) will be used. No RB/SF data can be obtained prior to Day –22.



*If RB/SF data are not available, data from the preceding day (Day –21) will be used.

Scenario 2: Sufficient e-Diary Data Available prior to Endoscopy at Day –4

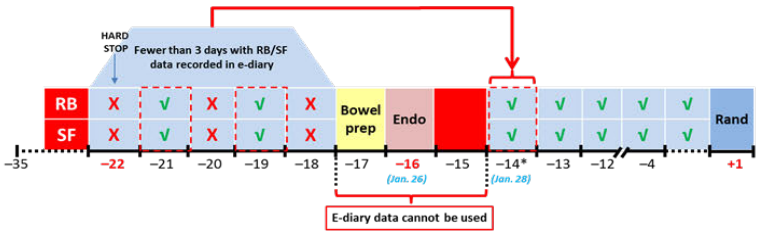
The e-diary data from the 3 consecutive days immediately preceding the bowel preparation day (Day –5 in this scenario) are used to derive RB and SF data for MCS calculation (Day –6 to Day –8, highlighted with red dashed lines in the figure). If e-diary data from these days are missing, RB/SF data from the preceding days (Days –9 to Day –22) will be used. No RB/SF data can be obtained prior to Day –22.



*If RB/SF data are not available, data from the preceding day (Day –9) will be used.

Scenario 3: Insufficient e-Diary Data Available prior to Endoscopy at Day –16

Only in cases where < 3 days of e-diary data are available prior to the bowel preparation day (Day –18 to Day –22 in this scenario), supplement with e-diary data starting 2 days after the endoscopy (e.g., January 28 if the endoscopy was performed on January 26). In the figure, the days highlighted with red dashed lines can be used for MCS calculation.



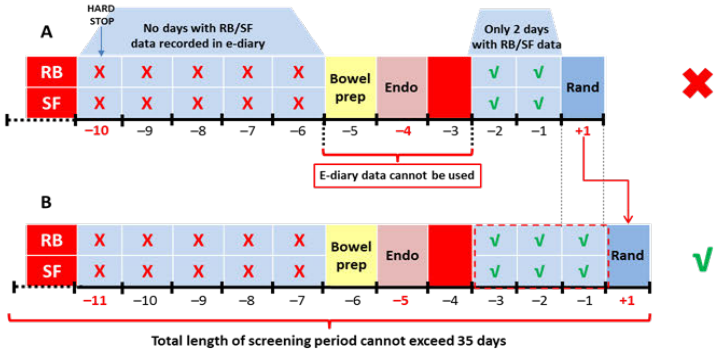
*If RB/SF data are not available, data from the next day (Day –13) will be used.

√ Day with RB/SF data recorded in e-diary.

X Day with RB/SF data not recorded in e-diary.

Scenario 4: Shorter Screening Period: Insufficient e-Diary Data Available prior to and after Endoscopy at Day –4

With a shorter screening period, there may be insufficient e-diary data (< 3 days total) available prior to the bowel preparation day (Day –6 to Day –10 in this scenario) and between the endoscopy and randomization (Day –2 and Day –1). Only in such cases, the randomization visit must be delayed by at least 1 day by extending the screening period after the endoscopy (screening period must remain ≤ 35 days) so sufficient data can be recorded in the e-diary (on Day –1 in the extended screening period in Figure B). In the schema, the days highlighted with red dashed lines can be used for MCS calculation.



Appendix 4
Mayo Clinic Score Measurement (cont.)

MCS =Mayo Clinic Score; RND =randomization; RB =rectal bleeding; SF =stool frequency.

Notes:

- If 3 days of e-diary data are available between Day −22 (inclusive) and bowel preparation, use e-diary data from the 3 most recent days prior to the bowel preparation day.
- Up to 3 days of post-endoscopy e-diary data, starting 2 days after the endoscopy, may be used, but ONLY when < 3 days of e-diary data are available between Day −22 and bowel preparation.
- If 2 days of e-diary data are available between Day −22 and bowel preparation, use those data and supplement with data from the first available e-diary entry after the endoscopy, starting 2 days after the endoscopy.
- If 1 day of e-diary data is available between Day −22 and bowel preparation, use those data and supplement with data from the first two available e-diary entries after the endoscopy, starting 2 days after the endoscopy.
- If 0 days of e-diary data are available between Day −22 and bowel preparation, use data from the first three available e-diary entries after the endoscopy, starting 2 days after the endoscopy.

Derivation of stool frequency and rectal bleeding subscores at re-screening in circumstances where a second endoscopy is not required:

In cases of screen failure, patients whose endoscopy was performed during screening will not undergo a second endoscopic procedure at re-screening, provided this was performed within 28 days from the new enrollment day and all endoscopy-related inclusion criteria have been met (see Section 4.7.2.1.2). For these patients, the RB and SF e-diary data will be taken from the 3 most recent consecutive days prior to the new enrollment day (i.e. Days −1, −2, and −3). Any missing day or days will be supplemented with the immediate next day or days recorded up to 22 days prior to the new enrollment day (e.g., if Day −2 is missing, Days −1, −3, and −4 will be used).

Appendix 4
Mayo Clinic Score Measurement (cont.)

PARTIAL MAYO CLINIC SCORE

The partial Mayo Clinic Score is identical to the Mayo Clinic Score BUT EXCLUDES THE ENDOSCOPY SUBSCORE

- Timepoints for partial Mayo Clinic Score can be found in the protocol schedule of assessments

Partial MCS is also required at time of suspected clinical relapse. If partial MCS $\geq$3 points compared to Week 10 AND absolute partial MCS $\geq$5 an endoscopy would be conducted and endoscopy subscore and full MCS calculated

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 5
PML Subjective and Objective Checklists

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 schedule of assessments (see Appendix 1). This neurologic exam will consist of administration of the PML Subjective Checklist and the PML Objective Checklist.

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

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

Appendix 5
PML Subjective and Objective Checklists (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 5
PML Subjective and Objective Checklists (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 5
PML Subjective and Objective Checklists (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 5
PML Subjective and Objective Checklists (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 5
PML Subjective and Objective Checklists (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).

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

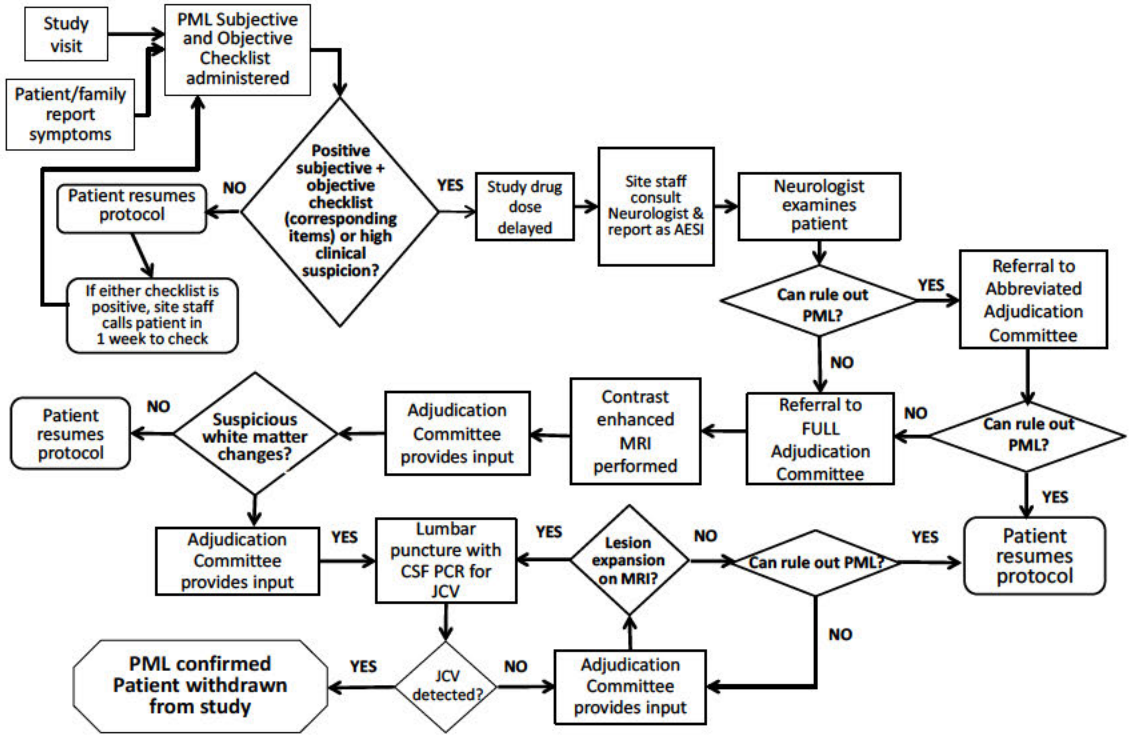
- *(ONLY* if the patient has subjective complaints about their memory or thinking) test the ability of the patient to recall 3 objects over 1 minute with distraction.

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 6
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 7
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 8
Clinical Criteria for Diagnosing Anaphylaxis

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

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

AND AT LEAST ONE OF THE FOLLOWING:

- Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

- Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
- Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced blood pressure or associated symptoms (e.g., hypotonia, syncope, incontinence)
- - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):

- Infants and children: low systolic blood pressure (age specific)[2] or greater than 30% decrease in systolic blood pressure
- Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline

---

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

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

Appendix 9
Quality of Life in Inflammatory Bowel Disease Questionnaire (IBDQ)

The Inflammatory Bowel Disease Questionnaire[2] (IBDQ)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

16 How often during the last 2 weeks have you had to avoid attending events where there was no washroom (bathroom, toilet) close to hand?
Please choose an option from:

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

17 Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas?
Please choose an option from:

A major problem	1
A big problem	2
A significant problem	3
Some trouble	4
A little trouble	5
Hardly any trouble	6
No trouble	7

18 Overall, in the last 2 weeks, how much of a problem have you had in maintaining, or getting to, the weight you would like to be at?
Please choose an option from:

A major problem	1
A big problem	2
A significant problem	3
Some trouble	4
A little trouble	5
Hardly any trouble	6
No trouble	7

19 Many patients with bowel problems often have worries and anxieties related to their illness. Worries about getting cancer, never feeling any better and having a relapse. How often during the last 2 weeks have you felt worried or anxious? Please choose an option from:

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

20 How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating?
Please choose an option from:

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

21 How often during the last 2 weeks have you felt relaxed and free of tension?
Please choose an option from:

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

22 How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements?
Please choose an option from:

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

23 How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem?
Please choose an option from:

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

24 How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from:

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

25 How much of the time during the last 2 weeks have you felt tearful or upset?
Please choose an option from:

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

26 How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants?
Please choose an option from:

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

27 How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem?
Please choose an option from:

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

28 To what extent **has your bowel problem** limited sexual activity during the last 2 weeks?
Please choose an option from:

No sex as a result of bowel disease	1
Major limitation as a result of bowel disease	2
Moderate limitation as a result of bowel disease	3
Some limitation as a result of bowel disease	4
A little limitation as a result of bowel disease	5
Hardly any limitation as a result of bowel disease	6
No limitation as a result of bowel disease	7

29 How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach?
Please choose an option from:

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

30 How much of the time during the last 2 weeks have you felt irritable?
Please choose an option from:

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

31 How often during the past 2 weeks have you felt a lack of understanding from others?
Please choose an option from:

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

32 How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks?
Please choose one of the following options from:

Very dissatisfied, unhappy most of the time	1
Generally dissatisfied, unhappy	2
Somewhat dissatisfied, unhappy	3
Generally satisfied, pleased	4
Satisfied most of the time, happy	5
Very satisfied most of the time, happy	6
Extremely satisfied, could not have been more happy or pleased	7

Appendix 10
EuroQoL Five-Dimension (EQ-5D) Questionnaire

Health Questionnaire

(English version for the US)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today