Official Title: Phase III, Double-Blind, Placebo-Controlled, Multicenter Study of the Efficacy and Safety of Etrolizumab During Induction and Maintenance in Patients With Moderate to Severe Active Ulcerative Colitis Who Have Been Previously Exposed to TNF Inhibitors

NCT Number: NCT02100696

Document Date: Protocol Version 8: 11-July-2018

PROTOCOL

TITLE:	**PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF THE EFFICACY AND SAFETY OF ETROLIZUMAB DURING INDUCTION AND MAINTENANCE IN PATIENTS WITH MODERATE TO SEVERE ACTIVE ULCERATIVE COLITIS WHO HAVE BEEN PREVIOUSLY EXPOSED TO TNF INHIBITORS**
PROTOCOL NUMBER:	GA28950
VERSION NUMBER:	8
EUDRACT NUMBER:	2013-004278-88
IND NUMBER:	100366
TEST PRODUCT:	Etrolizumab (PRO145223, RO5490261)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 12 November 2013
DATES AMENDED:	Version 2: 23 January 2014 Version 3: 11 March 2014 Version 4: 29 May 2014 Version 5: 27 September 2015, 7 December 2015 (VHP) Version 6: 18 November 2016 Version 7: 2 September 2017 Version 8: See electronic date stamp below.

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	11-Jul-2018 05:42:19

PROTOCOL AMENDMENT, VERSION 8:
RATIONALE

Protocol GA28950 has primarily been amended to reflect changes in efficacy endpoints. The changes will not impact study conduct at the site level. These changes are as follows:

- The primary efficacy endpoint for the Maintenance Phase has been changed to remission at Week 66 for patients who achieve clinical response (rather than remission) at Week 14. This change has been made to align with clinical practice standards whereby patients who experience a clinical response during treatment induction continue on treatment and are assessed for remission at a later time point (Sections 2.1, 3.4.1,6.1, 6.4 and 6.4.1, Figure 1 and Figure 3).
- To assess the onset of action of etrolizumab, a secondary efficacy endpoint of change in Mayo Clinic Score (MCS) rectal bleeding and stool frequency subscores from baseline to Week 6 has been added (Sections 2.1, 3.4.1, and 6.4.2).
- Secondary and exploratory efficacy endpoints have been amended to align with the revision of the primary efficacy endpoint (Sections 2.1, 3.4.1 and 6.4.2).
- Histologic remission, defined as a Nancy histological index of ≤ 1, has been added as a secondary efficacy outcome measure. The definition is based on consensus guidelines recommending that histologic remission should be defined by the absence of neutrophils in the crypts and lamina propria (Section 2.1, 3.4.1, 6.4.2 Appendix 12 and Table 1).
- The study sample size has been reduced from 800 to 605 patients as a result of the change in the Maintenance Phase primary efficacy endpoint, which will be powered at >90%. The Induction Phase primary efficacy endpoint definition (proportion of patients in remission at Week 14) will remain unchanged, but the reduction in sample size will lead to a drop in power from >90% to 80% (Sections 3.1.1, 6.1, 9.4, and Figure 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, 4.3.2.2, and 4.4.2).
- 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 is no longer an investigational product (Section 4.1.2).
- The exclusion criterion related to eligibility following receipt of investigational treatments has been modified to account for current molecules in development for the treatment of inflammatory bowel disease. The allowable time period after treatment has been reduced to 5 half-lives of the investigational product or 28 days after the last dose, (whichever is greater) prior to Day 1 of the study (Section 4.1.2).

- Derivation of the MCS endoscopic subscore at post-baseline timepoints has been amended to be consistent with emerging normative standards of endoscopic assessment in clinical trials (Sandborn et al. 2017). The sigmoid colon MCS endoscopic subscore will be used (rather than the score from the worst affected segment, i.e., rectum, sigmoid colon, or descending colon) if the baseline sigmoid colon MCS endoscopic subscore is 2–3. The sigmoid colon MCS endoscopic subscore is considered to be more reliable in assessing earlier treatment response (Section 4.6.1.4 and Appendix 3).
- Histologic activity on colon biopsies will be measured using the Nancy histological index instead of the Geboes scale. The Geboes scale was designed to characterize all types of mucosal inflammation related to ulcerative colitis but was not designed to easily compare differences in histologic activity over time in the context of a clinical trial. On the other hand, the Nancy histological index was developed and validated to capture meaningful changes in key histologic features of ulcerative colitis and can be easily applied in a clinical trial setting (Sections 4.6.1.5 and Appendix 12).
- Language regarding local injection-site reactions has been clarified in Table 5, "Guidelines for Managing Specific Adverse Events" (Section 5.1.2).
- 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).
- Language has been add to Section 6.1 to clarify that for the purpose of statistical analyses and sample size calculations, the Induction and Maintenance Phases will be treated as two independent studies, and as such, no adjustment to alpha is required.

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

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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, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF THE EFFICACY AND SAFETY OF ETROLIZUMAB DURING INDUCTION AND MAINTENANCE IN PATIENTS WITH MODERATE TO SEVERE ACTIVE ULCERATIVE COLITIS WHO HAVE BEEN PREVIOUSLY EXPOSED TO TNF INHIBITORS**
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EUDRACT NUMBER:	2013-004278-88
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 objectives for this study are as follows:

- To evaluate the efficacy of etrolizumab (105 mg subcutaneous [SC] every 4 weeks [Q4W]) compared with placebo for the induction of remission, as determined by the Mayo Clinic Score (MCS) at Week 14
- *To evaluate the efficacy of etrolizumab (105 mg SC Q4W) compared with placebo for remission at Week 66 among patients with a clinical response at Week 14, as determined by the MCS*

The secondary efficacy objectives for this study are as follows:

Induction Phase

- To evaluate induction of clinical remission at Week 14
- To evaluate clinical response at Week 14
- To evaluate improvement in endoscopic appearance of the mucosa at Week 14
- To evaluate endoscopic remission at Week 14
- *To evaluate histologic remission at Week 14*
- *To evaluate onset of action, defined as change from baseline in rectal bleed subscore at Week 6*
- *To evaluate onset of action, defined as change from baseline in stool frequency subscore at Week 6*

- To evaluate change from baseline in UC bowel movement signs and symptoms at Week 14, as assessed by the Ulcerative Colitis–Patient-Reported Outcome Signs and Symptoms (UC-PRO/SS) measure
- To evaluate change from baseline in UC abdominal symptoms at Week 14, as assessed by the UC-PRO/SS measure
- To evaluate change from baseline in patient–reported health-related quality of life (QOL) at Week 14, as assessed by the Inflammatory Bowel Disease Questionnaire (IBDQ)

Maintenance Phase

- To evaluate clinical remission at Week 66 in patients in clinical remission at Week 14
- To evaluate clinical remission at Week 66
- *To evaluate remission at Week 66 among patients in remission at Week 14*
- To evaluate improvement in endoscopic appearance of the mucosa at Week 66
- *To evaluate histologic remission at Week 66*
- To evaluate endoscopic remission at Week 66
- To evaluate corticosteroid-free clinical remission at Week 66 (off corticosteroid for at least 24 weeks prior to Week 66) in patients who were receiving corticosteroids at baseline
- To evaluate corticosteroid-free remission at Week 66 (off corticosteroid for at least 24 weeks prior to Week 66) in patients who were receiving corticosteroids at baseline
- To evaluate change in UC bowel movement signs and symptoms from baseline to Week 66, as assessed by the UC-PRO/SS measure
- To evaluate change in UC abdominal symptoms from baseline to Week 66, as assessed by the UC–PRO/SS measure
- To evaluate change in patient–reported health-related QOL from baseline to Week 66, as assessed by the IBDQ

The exploratory efficacy objectives for this study are as follows:

- *To evaluate clinical response at Week 66 among patients with a clinical response at Week 14*
- *To evaluate remission achieved at Week 66 among patients in clinical remission at Week 14*
- To evaluate corticosteroid-free clinical remission at Week 66 (off corticosteroid for at least 12 weeks prior to Week 66) in patients who were receiving corticosteroids at baseline
- *To evaluate change in histologic disease activity from baseline to Week 14 and Week 66*
- *To evaluate improvement in histologic and/or endoscopic disease activity*
- To evaluate change in health utilities, as assessed by the EuroQoL Five-Dimension Questionnaire (EQ-5D), from baseline to Week 14 and Week 14 to Week 66
- To evaluate frequency and duration of hospitalizations from Week 14 to Week 66
- *To evaluate response, remission, and corticosteroid-free endpoints, as determined by the modified MCS (mMCS)*

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the overall safety and tolerability of etrolizumab compared with placebo during induction and maintenance therapy over a period of 66 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)

Pharmacokinetic Objectives

The pharmacokinetic (PK) assessment will be performed in all patients during the Induction Phase and in all patients who were randomized into the Maintenance Phase.

The PK objectives for this study are as follows:

- To evaluate etrolizumab serum concentration at the time of primary endpoint evaluation (Weeks 14 and 66) and at predose time in the steady state during the maintenance dosing period
- To evaluate the inter-individual variability and potential covariate effects on etrolizumab serum exposure

Exploratory Pharmacodynamic and Diagnostic Objectives

The exploratory pharmacodynamics (PD) and diagnostic objectives for this study are as follows:

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

Study Design

Description of Study

This is a multicenter, Phase III, double-blind, placebo-controlled study evaluating the safety, efficacy, and tolerability of etrolizumab during induction and maintenance of remission compared with placebo in the treatment of moderately to severely active 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 severity will be measured using the MCS (see protocol), which is the current outcome measure accepted by regulatory authorities for drug development in UC. The target population is 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 the protocol, a rectal bleeding subscore ≥ 1, and a stool frequency subscore of ≥ 1), and involvement that extends a minimum of 20 cm from the anal verge.

Patients who are on background immunosuppressant therapy (6-mercaptopurine [MP], azathioprine [AZA], methotrexate [MTX]) may be enrolled if they have received a stable dose for at least 8 weeks prior to Day 1. Such patients should continue on stable doses of their background immunosuppressant therapy during 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 recently been initiated, the dose has to be stable for at least 4 weeks immediately prior to Day 1
- If corticosteroids are being tapered, the dose has to be stable for at least 2 weeks immediately prior to Day 1

Such patients should continue stable doses of their background corticosteroid until Week 14, at which point a corticosteroid taper will be initiated.

Initiation of corticosteroid or an increase in corticosteroid dose above the patients' entry dose (up to a maximum of 30 mg/day prednisone [or equivalent]) will not be permitted during screening. Use of budesonide will be allowed at stable doses ($\leq$ 9 mg) if the dose has been stable for $\geq$ 4 weeks prior to Day 1. Oral 5-aminosalicylate (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 $\geq$ 4 weeks and $\geq$ 2 weeks, respectively, prior to Day 1. Certain concomitant treatments are prohibited (see protocol for list of all prohibited concomitant treatments). Patients must have discontinued TNF inhibitor treatment and topical treatments for UC at least 8 weeks and 2 weeks prior to Day 1, respectively.

The study will be divided into:

- Screening period of up to 35 days during which patient eligibility will be determined
- Induction Phase of 14 weeks (Cohort 1: open-label etrolizumab treatment; Cohort 2: randomized to etrolizumab or placebo)
- Randomization of etrolizumab responders prior to a double-blind Maintenance Phase of 52 weeks or continued blinded treatment with placebo Q4W for 52 weeks for placebo induction responders
- Safety follow-up period of 12 weeks

A total of approximately 605 patients will be recruited from approximately 225 sites via an open-label induction arm (Cohort 1, n = 130) and a double-blind induction arm (Cohort 2, n = 475), which will be enrolled sequentially.

Cohort 1 patients will receive open-label etrolizumab 105 mg SC Q4W during the 14-week Induction Phase. Cohort 2 patients will be randomized in a 4:1 ratio to 105 mg etrolizumab SC Q4W (n ≈ 380) or placebo (n ≈ 95) during the 14-week Induction Phase. Randomization will be stratified by concomitant treatment with corticosteroids (including budesonide) (yes/no), concomitant treatment with immunosuppressants (yes/no), and disease activity measured during screening (MCS $\leq$ 9/MCS $\geq$ 10).

Eligibility for entry into the Maintenance Phase will be determined between Weeks 14 and 16. Patients in the etrolizumab arm of Cohort 2 who achieved a clinical response at Week 14 (see protocol for definition of clinical response) and all Week 14 clinical responders in Cohort 1 will be randomized into the Maintenance Phase and will receive either etrolizumab (105 mg SC Q4W) or placebo in a 1:1 ratio. Randomization will be stratified by remission status at Week 14, concomitant treatment with corticosteroids (including budesonide) at baseline, disease activity measured during screening (MCS $\leq$ 9/MCS $\geq$ 10), and induction cohort (Cohort 1/Cohort 2). It is estimated that the planned approximately 510 etrolizumab patients from Cohort 1 and Cohort 2 will provide approximately 154 patients in clinical response for randomization into the Maintenance Phase. Additional patients may be enrolled into Cohort 1, if needed, to achieve a $sufficient$ number of patients in the Maintenance Phase.

Patients initially randomized to placebo will also be assessed for clinical response at Week 14. Patients achieving a clinical response will continue to receive blinded placebo during the Maintenance Phase of the study. Patients in either Cohort 1 or Cohort 2, who do not achieve clinical response at Week 14, patients who have clinical relapse during the Maintenance Phase, patients who receive defined rescue treatment, and patients who complete 66 weeks of the study may be given the option of enrolling into Part 1 (OLE) of Study GA28951, where they will receive open-label etrolizumab treatment, if eligible. If patients choose not to enroll in Part 1 (OLE) of Study GA28951, they will enter the 12-week safety follow-up period of this study and then will be requested to enroll in Part 2 (SM) of Study GA28951 for 92 weeks of extended PML monitoring.

Study Drug Administration

The first two doses of study medication 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 his or her caregiver in the clinic; if deemed appropriate by the HCP, the remaining doses of 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 is provided in the protocol). The administration of the study medication at home by the patients or their caregivers will occur after their 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.

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 14 for 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 $\leq$ 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 14, patients receiving budesonide who achieve clinical response at Week 14 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 corticosteroid withdrawal, corticosteroid dose may be increased (up to the dose at study entry if required), but tapering must begin again within 2 weeks.

Immunosuppressants during the Study

Patients <u>should continue</u> stable doses of immunosuppressants throughout 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.

Clinical relapse is defined as an:

- Increase in partial Mayo Clinic Score (pMCS) $\geq$ 3 points compared to induction timepoint (Week 14) AND absolute pMCS $\geq$ 5 AND endoscopic subscore $\geq$ 2

If a patient meets criteria for clinical relapse during the Maintenance Phase of the study, he or she may withdraw from this study and enroll in Part 1 (OLE) of Study GA28951 if eligible.

Rescue Therapy That <u>Can</u> be Given with Study Medication for the Treatment of UC

<u>During the Induction Phase (prior to Week 14)</u>

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

In the Induction Phase, any patient who requires initiation of an immunosuppressant (AZA, 6-MP, or MTX), oral or topical 5-ASA, or corticosteroid, or increase in dose over baseline levels for treatment of worsening disease symptoms, should stay in the study until Week 14, at which time the patient can enroll in Part 1 (OLE) of Study GA28951 to receive open-label etrolizumab, if eligible, or enter the 12-week safety follow-up of this study and then enroll in Part 2 (SM) of Study GA28951 for extended PML monitoring. These patients will be classified as non-responders at Week 14 and may not continue into the Maintenance Phase of the trial.

<u>During the Maintenance Phase</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.

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 enroll in Part 1 (OLE) of Study GA28951, if eligible, based on the investigator's discretion. Patients who leave the treatment period early to enroll in Part 1 (OLE) of Study GA28951 should complete the early withdrawal from treatment visit prior to enrollment in Study GA28951.

Patients must begin the specified corticosteroid taper at Week 14 during the Maintenance Phase. For patients who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms of either UC or corticosteroid 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 blinded study.

Patients who were not receiving corticosteroids at baseline and patients who have completed the corticosteroid 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 corticosteroid withdrawal may remain in the blinded study or may enroll in Part 1 (OLE) of Study GA28951, if eligible, based on the investigator's discretion. Patients who leave the treatment period early to enroll in Part 1 (OLE) of Study GA28951 should complete the early withdrawal from treatment visit prior to enrollment in Study GA28951.

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 be given the option to enroll in Part 1 (OLE) of Study GA28951, if eligible, based on the investigator's discretion. Patients who leave the treatment period early to enroll in Part 1 (OLE) of Study GA28951 should complete the early withdrawal from treatment visit prior to enrollment in Study GA28951.

Endoscopy to document disease activity for patients exiting the treatment period early for any reason is strongly recommended.

Rescue Therapy That <u>Cannot</u> be Given with Study Medication for the Treatment of UC

At ANY time during the conduct of the trial, 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), anti-adhesion molecules, *Janus kinase (JAK) inhibitors,* cyclosporine, tacrolimus, or investigational agents are 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 the protocol). These patients will also be requested to enroll in Part 2 (SM) of Study GA28951 for 92 weeks of extended PML monitoring.

A complete list of study visits and assessments can be found in the Schedule of Assessments (see the protocol for further details). A complete list of eligibility for transfer of patients to OLE-SM and 12-week safety follow-up is in the protocol.

Number of Patients

A total of approximately 605 patients will be enrolled from approximately 225 sites via an open-label induction arm (Cohort 1, n = 130) and a double-blind induction arm (Cohort 2, n = 475).

Cohort 2 patients will be randomized in a 4:1 ratio to etrolizumab 105 mg SC (n ≈ 380) or placebo (n ≈ 95) Q4W. Patients in the etrolizumab arm of Cohort 2 who achieved a clinical response at Week 14 (see protocol for definition of clinical response) and all Week 14 clinical responders in Cohort 1 will be randomized into the Maintenance Phase and will receive either etrolizumab (105 mg SC Q4W) or placebo in a 1:1 ratio. It is estimated that the planned approximately 510 etrolizumab patients from Cohort 1 and Cohort 2 will provide approximately 154 patients in clinical response for randomization into the Maintenance Phase. Additional patients may be enrolled into Cohort 1, if needed, to meet sample size requirements for the Maintenance Phase.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Treatment within 5 years prior to screening with one or two induction regimens that contain TNF inhibitors (including TNF inhibitor biosimilars), as defined below:
  - Infliximab: 5 mg/kg IV, 2 doses
  - Adalimumab: 160 mg SC followed by an 80-mg dose
  - Golimumab: 200 mg SC followed by a 100-mg dose

  Patients will be categorized as TNF inhibitor refractory, TNF inhibitor intolerant, or neither refractory nor intolerant to TNF inhibitors. TNF inhibitor refractory and TNF inhibitor intolerant are defined as follows:

  TNF inhibitor refractory: Persistent signs and symptoms of active disease despite TNF inhibitor treatment or recurrence of symptoms during maintenance TNF inhibitor treatment (i.e., following prior clinical benefit)

  TNF inhibitor intolerant: History of intolerance to TNF inhibitors, (including, but not limited to, injection-site reactions, congestive heart failure, or infection)
- Able and willing to provide written informed consent
- 18–80 years of age, inclusive
- Diagnosis of UC established at least 3 months prior to 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 $\geq$2 as determined by the central reading procedure described in the protocol, a rectal bleeding subscore $\geq$1, and a stool frequency subscore of $\geq$ 1 during the screening period (prior to Day 1). See the protocol for additional information regarding the 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 Day 1. See the protocol for additional information regarding the time window.
- Washout of TNF inhibitor therapy for at least 8 weeks preceding Day 1
- Any ongoing UC therapy must be at stable doses:

  May be receiving oral 5-ASA compounds provided that the dose has been stable for $\geq$ 4 weeks immediately prior to Day 1

  May be receiving oral corticosteroid therapy (prednisone at a stable dose of $\leq$ 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 Day 1. If corticosteroids are being tapered, the dose has to be stable for at least 2 weeks immediately prior to Day 1.

  May be receiving budesonide therapy at a stable dose of up to 9 mg a day for $\geq$ 4 weeks prior to Day 1

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

  May be receiving AZA, 6-MP, or MTX, provided that the dose has been stable for at least 8 weeks immediately prior to 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, a condom, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 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 protocol)

  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

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 intravenous (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 Day 1, except for AZA and 6-MP.
- Use of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil within 4 weeks prior to Day 1
- Chronic nonsteroidal anti-inflammatory drug (NSAID) use (Note: 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 $\leq$ 2 weeks prior to Day 1
- Apheresis (i.e., Adacolumn apheresis) within 2 weeks prior to 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 Day 1
- 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 $\geq$ 3 weeks prior to Day 1

<u>Exclusion Criteria Related to General Safety</u>

- 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 co-morbidity, such as cardiac (e.g., moderate to severe heart failure New York Heart Association class III/IV), pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders (excluding UC)
- Neurological 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 $\leq$ 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 , high-grade squamous intraepithelial lesions, or cervical intraepithelial neoplasia 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 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 has a known history of HCV antibody positivity with 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 HBV DNA test cannot be performed, the patient is not eligible for this study.

  If the HBV DNA test result 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 Day 1 or other intestinal pathogens (as assessed by stool culture and ova and parasite evaluation) within 30 days prior to Day 1
- Evidence of or treatment for clinically significant cytomegalovirus (CMV) colitis (based on the investigator's judgment) within 60 days prior to Day 1. Laboratory confirmation of CMV from colon biopsy is required during screening evaluation only if clinical suspicion is high and to determine the need for CMV treatment.
- History of active or latent 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 skin test or QuantiFERON®TB Gold test, see below) are not eligible for this study.

  Patients with a chest X-ray (posteroanterior and lateral) within 3 months of Day 1 suspicious for pulmonary TB are not eligible for this study.
- 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 Day 1

  Fungal infections of the nail beds

  Oral or vaginal candidiasis that has resolved with or without treatment prior to Day 1
- Any major episode of infection 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 Day 1
- History of organ transplant

Exclusion Criteria Related to Laboratory Abnormalities (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 66 weeks. Patients who do not achieve a clinical response at Week 14, patients who have clinical relapse during the Maintenance Phase, patients who receive defined rescue treatment, and patients who complete 66 weeks of the study may be given the option of enrolling into 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 study and then be requested to enroll in Part 2 (SM) of Study GA28951 for 92 weeks of monitoring for PML.

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

Outcome Measures

Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

Primary Efficacy Outcome Measures

Induction Phase

- Remission at Week 14, *as determined by the MCS*

Maintenance Phase

- Remission at Week 66 *among patients with a clinical response at Week 14, as determined by the MCS*

Secondary Efficacy Outcome Measures

Induction Phase

- Clinical remission at Week 14
- Clinical response at Week 14
- Improvement in endoscopic appearance of the mucosa at Week 14
- Endoscopic remission at Week 14
- *Histologic remission at Week 14*
- *Change from baseline in rectal bleed subscore at Week 6*
- *Change from baseline in stool frequency subscore at Week 6*
- Change from baseline in UC bowel movement signs and symptoms as assessed by the UC-PRO/SS measure at Week 14
- Change from baseline in UC abdominal symptoms as assessed by the UC-PRO/SS measure at Week 14
- Change from baseline in patients' health-related QOL at Week 14 as assessed by the overall score of the IBDQ

Maintenance Phase

- Clinical remission at Week 66 among patients in clinical remission at Week 14
- Clinical remission at Week 66
- *Remission at Week 66 among patients in remission at Week 14*
- Improvement in endoscopic appearance of the mucosa at Week 66
- *Histologic remission at Week 66*
- Endoscopic remission at Week 66
- Corticosteroid-free clinical remission at Week 66 (off corticosteroid for at least 24 weeks prior to Week 66) in patients who were receiving corticosteroids at baseline
- Corticosteroid-free remission at Week 66 (off corticosteroid for at least 24 weeks prior to Week 66) in patients who were receiving corticosteroids at baseline
- Change from baseline in UC bowel movement signs and symptoms as assessed by the UC-PRO/SS measure at Week 66
- Change from baseline in UC abdominal symptoms as assessed by the UC-PRO/SS measure at Week 66
- Change from baseline in patients' health-related QOL at Week 66 as assessed by the overall score of the IBDQ

Exploratory Efficacy Outcome Measures

- *Clinical response at Week 66 among patients with a clinical response at Week 14*
- *Remission at Week 66 among patients in clinical remission at Week 14*
- Corticosteroid-free clinical remission at Week 66 (off corticosteroid for at least 12 weeks prior to Week 66) in patients who are receiving corticosteroids at baseline
- *Histologic disease activity change from baseline to Week 14 and Week 66*
- *Improvement in histologic and/or endoscopic disease activity*
- Change in health utilities, as assessed by the EQ-5D, from baseline to Week 14 and Week 14 to Week 66
- Frequency and duration of hospitalizations from Week 14 to Week 66
- *Response, remission and corticosteroid-free endpoints as determined by the mMCS*

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
- Incidence and severity of hypersensitivity reaction events

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Serum trough concentration at steady-state during the dosing period from Week 16 to Week 66
- Serum concentration at primary endpoint time (Week 14 and Week 66)

Exploratory Biomarker Outcome Measures

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

- Remission at Week 14 and maintenance of remission at Week 66 in patients according to baseline levels of colonic tissue biomarkers and/or peripheral blood, including but not limited to αE integrin
- Changes in levels of exploratory colonic tissue and/or peripheral blood biomarkers during the Induction and Maintenance Phases
- 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

Investigational Medicinal Products

Test Product

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

Comparator

Placebo PFS: etrolizumab SC matching placebo given in the amount of 0.7 mL solution will be administered by SC injection Q4W.

Non-Investigational Medicinal Products

Patients are to continue on their baseline dose of corticosteroid (including budesonide) to the end of the Induction Phase (Week 14). Tapering of corticosteroid (including budesonide) is to be attempted during the Maintenance Phase.

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 discontinuing 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 the study.

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

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

Statistical Methods

Primary Analysis

For the purpose of statistical analyses, the Induction and Maintenance Phases will be treated as two independent studies. The analysis of the Induction Phase will formally evaluate the efficacy and safety of 105 mg etrolizumab SC Q4W versus placebo as an induction therapy.

The analysis of the Maintenance Phase will formally evaluate the efficacy and safety of 105 mg etrolizumab SC Q4W versus placebo as a maintenance therapy.

The analysis of data from the 66-week treatment period (Induction and Maintenance Phases) will be performed when all data from this period are in the database and data have been cleaned and verified.

Whereas Sponsor personnel will be unblinded to treatment assignment to perform the primary analyses, patients and study site personnel will remain blinded to individual treatment assignment (for Cohort 2 patients and those re-randomized into the Maintenance Phase) 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.

Determination of Sample Size

The study sample size was selected so that sufficient patients are enrolled to evaluate the primary endpoints in the blinded Induction Phase and the Maintenance Phase respectively. Approximately *605* patients will be enrolled in the open-label induction arm (Cohort 1, $n \approx 130$) or the blinded induction cohort (Cohort 2, $n \approx 475$).

Cohort 2 patients will be randomized in a 4:1 ratio to etrolizumab ($n \approx 380$) or placebo ($n \approx 95$). This will provide *approximately 80*% power to detect a 10% difference in remission rates at Week 14 between the etrolizumab and placebo arms, under the assumption of a placebo remission rate of $\leq 5\%$ and a two-sided χ^2 test at the 5% significance level.

The primary endpoint for the Maintenance Phase is Week 66 remission among patients *with a clinical response* at Week 14. *In total, it is estimated that approximately 154 etrolizumab patients will achieve clinical response at the end of the Induction Phase and therefore will be randomized in the Maintenance Phase, under the assumption of a Week 14 clinical response rate of approximately 30% in the pooled etrolizumab induction group.*

A sample size of 154 patients in the Maintenance Phase will provide >90% power to detect a 30% difference in remission rates between the two maintenance arms, under the assumption of a placebo Week 66 remission rate $\leq 10\%$ and a Fisher exact test at the 5% significance level.

The planned approximately *510* etrolizumab patients from Cohort 1 and Cohort 2 would provide approximately *154* patients *with a clinical response* at Week 14, under the assumption of a Week 14 *clinical response* rate of at least *30*% in the pooled (Cohort 1 and Cohort 2) etrolizumab induction group. Additional patients may be enrolled into Cohort 1, if needed, to achieve this target number of approximately *154* patients randomized into the Maintenance Phase.

For the purpose of statistical analyses and sample size calculations, the Induction and Maintenance Phases will be treated as two independent studies, and as such no adjustment to alpha is required.

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
DCSI	Development Core Safety Information
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

Abbreviation	Definition
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
IxRS	interactive voice/Web-based response system
JAK	*Janus kinase*
JCV	John Cunningham virus
LD	loading dose
MAb	monoclonal antibody
MAdCAM-Fc	mucosal addressin cell adhesion molecule fragment crystallizable region
MCS	Mayo Clinic Score
mMCS	*modified 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	pharmacodynamic
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
QOL	quality of life
qPCR	quantitative polymerase chain reaction
RCR	Roche Clinical Repository
SAP	Statistical Analysis Plan

Abbreviation	Definition
SC	subcutaneous
SM	safety monitoring
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor-alpha
TNF-IR	inadequate response to anti-tumor necrosis factor
UC	ulcerative colitis
UC-PRO/SS	Ulcerative Colitis Patient-Reported Outcome Signs and Symptoms
ULN	upper limit of normal

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 corticosteroid-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 corticosteroid dependent and only half maintain corticosteroid-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 corticosteroid-free remission, but efficacy in maintaining corticosteroid-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 corticosteroid 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 corticosteroid-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 IBD patients who have chronic disease (Hanauer et al. 2002; Sandborn et al. 2005; Feagan et al. 2013). Patients whose disease fails to respond to medical therapy may be treated with total proctocolectomy with an ileal pouch-anal anastomosis. Although surgical intervention may be curative, complications such as chronic pouchitis, fecal incontinence, or decreased female fertility can occur (Bradley and Oliva-Hemker 2012). The current treatments are associated with significant adverse events, resulting in low rates of sustained remission, or are highly invasive.

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

1.2 BACKGROUND ON ETROLIZUMAB

A new class of molecules targeting the integrin receptors that regulate leukocyte trafficking to specific tissues in the body have 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 Investigator's Brochure for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Although there are therapeutic options including TNF inhibitors, a significant proportion of patients with UC will not experience a durable clinical benefit with those treatment options. 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). 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 who have chronic disease (Hanauer et al. 2002; Sandborn et al. 2005; Feagan et al. 2013). As noted above, etrolizumab distinguishes itself from other anti-integrins on the basis of gut selectivity combined with a potential 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 leucocyte/lymphocyte in the intestinal mucosa.

No clinically significant safety signals were detected on administration of etrolizumab to patients with moderate to severe UC across a dose range of 0.3–10.0 mg*/kg* IV/SC in the single ascending dose stage and of 0.5–3.0 mg/kg SC and 4 mg/kg IV monthly for 3 doses in the multidose stage of the Phase I study or in the Phase II study of 120 patients.

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 moderate to severely active UC patients has been completed. Patients 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).

In EUCALYPTUS, etrolizumab showed clinically meaningful efficacy for both doses relative to placebo for the primary endpoint: 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. In the inadequate response to anti-tumor necrosis factor (TNF-IR) subgroup, which represents a refractory population with limited treatment options, clinical remission at Week 10 was observed in 4.5% of the $100\ mg$ etrolizumab group, 4% of the 300 mg + LD group, and in 0% of the placebo group, respectively. However, data from SPRUCE (OLE Study GA27927) suggests that with longer duration of treatment, gut mucosal-selective anti-trafficking agents do benefit this patient population over time (Feagan et al. 2012). With 4 additional weeks of follow-up in OLE, clinically meaningful efficacy was observed:

- 31% (10 of 32) of TNF-IR patients who had not responded to etrolizumab by Week 10 and rolled into the OLE achieved clinical response by partial Mayo Clinic Score (pMCS) at 14 weeks
- 9% (3 of 32) of TNF-IR patients who had not responded to etrolizumab by Week 10 and rolled into the OLE achieved clinical remission by pMCS at 14 weeks

The present study is powered to detect a 10% difference in induction of remission rates between etrolizumab and placebo-treated patients. Given that patients failing TNF inhibitor therapy have very limited treatment options available to them, the TNF-IR patient population represent an unmet medical need population. Consequently, the potential benefits of etrolizumab in this population warrant further investigation.

In summary, favorable safety (see Section 1.2) and efficacy data were observed in the Phase II EUCALYPTUS study and in the OLE study (SPRUCE). Overall, etrolizumab showed compelling efficacy compared with placebo and there were no clinically significant safety signals. Additionally, etrolizumab distinguishes itself from vedolizumab by blocking $\alpha E\beta 7$ in addition to $\alpha 4\beta 7$, which is involved in lymphocyte retention and may contribute to its efficacy and/or safety profile. Etrolizumab is a gut-selective anti-trafficking agent and does not bind to $\alpha 4\beta 1$ (target for natalizumab), which regulates trafficking to both mucosal and non-mucosal tissues, including the CNS. Although natalizumab has been associated with an increased risk of PML, no events of PML to date have been reported during 2-year PML extensive monitoring in the Phase II study, EUCALYPTUS, and OLE SPRUCE study.

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

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

The primary efficacy objectives for this study are as follows:

- To evaluate the efficacy of etrolizumab (105 mg SC every 4 weeks [Q4W]) compared with placebo for the induction of remission, as determined by the MCS at Week 14
- *To evaluate the efficacy of etrolizumab (105 mg SC Q4W) compared with placebo for remission at Week 66 among patients with a clinical response at Week 14, as determined by the MCS*

The secondary efficacy objectives for this study are as follows:

Induction Phase

- To evaluate induction of clinical remission at Week 14
- To evaluate clinical response at Week 14
- To evaluate improvement in endoscopic appearance of the mucosa at Week 14
- To evaluate endoscopic remission at Week 14
- *To evaluate histologic remission at Week 14*
- *To evaluate onset of action, defined as change from baseline in rectal bleed subscore at Week 6*
- *To evaluate onset of action, defined as change from baseline in stool frequency subscore at Week 6*
- To evaluate change from baseline in UC bowel movement signs and symptoms at Week 14, as assessed by the Ulcerative Colitis–Patient-Reported Outcome Signs and Symptoms (UC-PRO/SS) measure
- To evaluate change from baseline in UC abdominal symptoms at Week 14, as assessed by the UC-PRO/SS measure
- To evaluate change from baseline in patient–reported health-related QOL at Week 14, as assessed by the Inflammatory Bowel Disease Questionnaire (IBDQ)

Maintenance Phase

- To evaluate clinical remission at Week 66 in patients in clinical remission at Week 14
- To evaluate clinical remission at Week 66
- *To evaluate remission at Week 66 among patients in remission at Week 14*
- To evaluate improvement in endoscopic appearance of the mucosa at Week 66
- *To evaluate histologic remission at Week 66*
- To evaluate endoscopic remission at Week 66

- To evaluate corticosteroid-free clinical remission at Week 66 (off corticosteroid for at least 24 weeks prior to Week 66) in patients who were receiving corticosteroids at baseline
- To evaluate corticosteroid-free remission at Week 66 (off corticosteroid for at least 24 weeks prior to Week 66) in patients who were receiving corticosteroids at baseline
- To evaluate change in UC bowel movement signs and symptoms from baseline to Week 66, as assessed by the UC-PRO/SS measure
- To evaluate change in UC abdominal symptoms from baseline to Week 66, as assessed by the UC–PRO/SS measure
- To evaluate change in patient–reported health-related QOL from baseline to Week 66, as assessed by the IBDQ

The exploratory efficacy objectives for this study are as follows:

- *To evaluate clinical response at Week 66 among patients with a clinical response at Week 14*
- *To evaluate remission achieved at Week 66 among patients in clinical remission at Week 14*
- To evaluate corticosteroid-free clinical remission at Week 66 (off corticosteroid for at least 12 weeks prior to Week 66) in patients who were receiving corticosteroids at baseline
- *To evaluate change in histologic disease activity from baseline to Week 14 and Week 66*
- *To evaluate improvement in histologic and/or endoscopic disease activity*
- To evaluate change in health utilities, as assessed by the EuroQoL Five-Dimension Questionnaire (EQ-5D), from baseline to Week 14 and Week 14 to Week 66
- To evaluate frequency and duration of hospitalizations from Week 14 to Week 66
- *To evaluate response, remission, and corticosteroid-free endpoints, as determined by the mMCS*

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 PGA
Partial MCS	pMCS is a composite of 3 assessments of the MCS, each rated from 0–3: stool frequency, rectal bleeding, and PGA
Modified MCS	*mMCS is a composite of 3 assessments of the MCS, each rated from 0–3: stool frequency, rectal bleeding, and endoscopy*
Remission	MCS $\leq$ 2 with individual subscores $\leq$ 1 and a rectal bleeding subscore of 0
Maintained remission	Remission achieved at the start of the Maintenance Phase (Week 14) and maintained at the end of the Maintenance Phase (Week 66).
Clinical remission	MCS $\leq$ 2 with individual subscores $\leq$ 1
Maintained clinical remission	Clinical remission achieved at the start of the Maintenance Phase (Week 14) and maintained at the end of the Maintenance Phase (Week 66)
Clinical response	MCS with $\geq$ 3-point decrease and 30% reduction from baseline as well as $\geq$ 1-point decrease in rectal bleeding subscore or an absolute rectal bleeding score of 0 or 1
Corticosteroid-free clinical remission	Clinical remission with no corticosteroid use for 12 or 24 weeks prior to Week 66
Corticosteroid-free remission	Remission with no corticosteroid use for 24 weeks prior to Week 66
Improvement in endoscopic appearance of the mucosa	Endoscopic subscore $\leq$ 1
Endoscopic remission	Endoscopic subscore = 0
Histologic remission	*NHI $\leq$1*

MCS = Mayo Clinic Score; *mMCS = modified Mayo Clinic Score*; PGA = Physician's Global Assessment; pMCS = partial Mayo Clinic Score*; NHI = Nancy histological index.*

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2.2 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the overall safety and tolerability of etrolizumab compared with placebo during induction and maintenance therapy over a period of 66 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)

2.3 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) assessment will be performed in all patients during the Induction Phase and in all patients who were randomized into the Maintenance Phase.

The PK objectives for this study are as follows:

- To evaluate etrolizumab serum concentration at the time of primary endpoint evaluation (Weeks 14 and 66) and at predose time in the steady state during the maintenance dosing period
- To evaluate the inter-individual variability and potential covariate effects on etrolizumab serum exposure

2.4 EXPLORATORY PHARMACODYNAMIC AND DIAGNOSTIC OBJECTIVES

The exploratory pharmacodynamics (PD) and diagnostic objectives for this study are as follows:

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

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is a multicenter, Phase III, double-blind, placebo-controlled study evaluating the safety, efficacy, and tolerability of etrolizumab during induction and maintenance of remission compared with placebo in the treatment of moderately to severely active 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 severity will be measured using the MCS (see Appendix 3), which is the current outcome measure accepted by regulatory authorities for drug development in UC. The target population is 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 4.6.1.4, a rectal bleeding subscore ≥1, and a stool frequency subscore of ≥1) and involvement that extends a minimum of 20 cm from the anal verge.

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 Day 1. Such patients should continue on stable doses of their background immunosuppressant therapy during 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 recently been initiated, the dose has to be stable for at least 4 weeks immediately prior to Day 1
- If corticosteroids are being tapered, the dose has to be stable for at least 2 weeks immediately prior to Day 1

Such patients should continue stable doses of their background corticosteroid until Week 14, at which point a corticosteroid taper will be initiated.

Initiation of corticosteroid or an increase in corticosteroid dose above the patients' entry dose (up to a maximum of 30 mg/day prednisone [or equivalent]) will not be permitted during screening. Use of budesonide will be allowed at stable doses ($\leq$ 9 mg) if the dose has been stable for $\geq$ 4 weeks prior to 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 $\geq$ 4 weeks and $\geq$ 2 weeks, respectively, prior to Day 1. Certain concomitant treatments are prohibited (see Section 4.1.2 for list of all prohibited concomitant treatments). Patients must have discontinued TNF inhibitor treatment and topical treatments for UC at least 8 weeks and 2 weeks prior to Day 1, respectively.

The study will be divided into:

- Screening period of up to 35 days during which patient eligibility will be determined (for details see Section 4.6.2.1)
- Induction Phase of 14 weeks (Cohort 1: open-label etrolizumab treatment; Cohort 2: randomized to etrolizumab or placebo)
- Randomization of etrolizumab responders prior to a double-blind Maintenance Phase of 52 weeks or continued blinded treatment with placebo Q4W for 52 weeks for placebo induction responders
- Safety follow-up period of 12 weeks

A total of approximately 605 patients will be recruited (see Figure 1) from approximately 225 sites via an open-label induction arm (Cohort 1, n = 130) and a double-blind induction arm (Cohort 2, n = 475), which will be enrolled sequentially.

Cohort 1 patients will receive open-label etrolizumab 105 mg SC Q4W during the 14-week Induction Phase. Cohort 2 patients will be randomized in a 4:1 ratio to 105 mg etrolizumab SC Q4W (n $\approx$ 380) or placebo (n $\approx$ 95) during the 14-week Induction Phase. Randomization will be stratified by concomitant treatment with corticosteroids (including budesonide) (yes/no), concomitant treatment with immunosuppressants (yes/no), and disease activity measured during screening (MCS $\leq$ 9/MCS $\geq$ 10).

Eligibility for entry into the Maintenance Phase will be determined between Weeks 14 and 16. Patients in the etrolizumab arm of Cohort 2 who achieved a clinical response at Week 14 (see Table 1 for definition of clinical response) and all Week 14 clinical responders in Cohort 1 will be randomized into the Maintenance Phase and will receive either etrolizumab (105 mg SC Q4W) or placebo in a 1:1 ratio. Randomization will be stratified by remission status at Week 14, concomitant treatment with corticosteroids (including budesonide) at baseline, disease activity measured during screening (MCS $\leq$ 9/MCS $\geq$ 10), and induction cohort (Cohort 1/Cohort 2). It is estimated that the planned approximately 510 etrolizumab patients from Cohort 1 and Cohort 2 will provide approximately 154 patients in clinical response for randomization into the Maintenance Phase. Additional patients may be enrolled into Cohort 1, if needed, to achieve a $sufficient$ number of patients in the Maintenance Phase.

Patients initially randomized to placebo will also be assessed for clinical response at Week 14. Patients achieving a clinical response will continue to receive blinded placebo during the Maintenance Phase of the study. Patients in either Cohort 1 or Cohort 2, who do not achieve clinical response at Week 14, patients who have clinical relapse during the Maintenance Phase, patients who receive defined rescue treatment (see Section 4.3.2.2), and patients who complete 66 weeks of the study may be given the option of enrolling into Part 1 (OLE) of Study GA28951, where they will receive open-label etrolizumab treatment, if eligible. If patients choose not to enroll in Part 1 (OLE) of Study GA28951, they will enter the 12-week safety follow-up period of this study and then will be requested to enroll in Part 2 (SM) of Study GA28951 for 92 weeks of extended PML monitoring.

Study Drug Administration

The first two doses of study medication 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 his or her caregiver in the clinic; if deemed appropriate by the HCP, the remaining doses of 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 is provided in Section 5.1.5). The administration of the study medication at home by the patients or their caregivers will occur after their 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 4.3.2.

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 14 for 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 14, patients receiving budesonide who achieve clinical response at Week 14 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 corticosteroid withdrawal, corticosteroid dose may be increased (up to the dose at study entry if required), but tapering must begin again within 2 weeks.

Immunosuppressants during the Study

Patients <u>should continue</u> stable doses of immunosuppressants throughout 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 Definition of Clinical Relapse

Clinical relapse is defined as an:

- Increase in partial Mayo Clinic Score (pMCS) $\geq$ 3 points compared to induction timepoint (Week 14) AND absolute pMCS $\geq$5 AND endoscopic subscore $\geq$2

If a patient meets criteria for clinical relapse during the Maintenance Phase of the study, he or she may withdraw from this study and enroll in Part 1 (OLE) of Study GA28951 if eligible.

3.1.1.2 Rescue Therapy

Rescue Therapy That <u>Can</u> Be Given with Study Medication for the Treatment of UC

During the Induction Phase (prior to Week 14)

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

In the Induction Phase, any patient who requires initiation of an immunosuppressant (AZA, 6-MP, or MTX), oral or topical 5-ASA, or corticosteroid, or increase in dose over baseline levels for treatment of worsening disease symptoms, should stay in the study until Week 14, at which time the patient can enroll in Part 1 (OLE) of Study GA28951 to receive open-label etrolizumab, if eligible, or enter the 12-week safety follow-up of this study and then enroll in Part 2 (SM) of Study GA28951 for extended PML monitoring. These patients will be classified as non-responders at Week 14 and may not continue into the Maintenance Phase of the trial.

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 may continue blinded treatment.

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 enroll in Part 1 (OLE) of Study GA28951, if eligible, based on the investigator's discretion. Patients who leave the treatment period early to enroll in Part 1 (OLE) of Study GA28951 should complete the early withdrawal from treatment visit prior to enrollment in Study GA28951.

Patients must begin the specified corticosteroid taper at Week 14 during the Maintenance Phase. For patients who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms of either UC or corticosteroid 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 blinded study.

Patients who were not receiving corticosteroids at baseline and patients who have completed the corticosteroid 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 corticosteroid withdrawal may remain in the blinded study or may enroll in Part 1 (OLE) of Study GA28951, if eligible, based on the investigator's discretion. Patients who leave the treatment period early to enroll in Part 1 (OLE) of Study GA28951 should complete the early withdrawal from treatment visit prior to enrollment in Study GA28951.

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 be given the option to enroll in Part 1 (OLE) of Study GA28951, if eligible, based on the investigator's discretion. Patients who leave the treatment period early to enroll in Part 1 (OLE) of Study GA28951 should complete the early withdrawal from treatment visit prior to enrollment in Study GA28951.

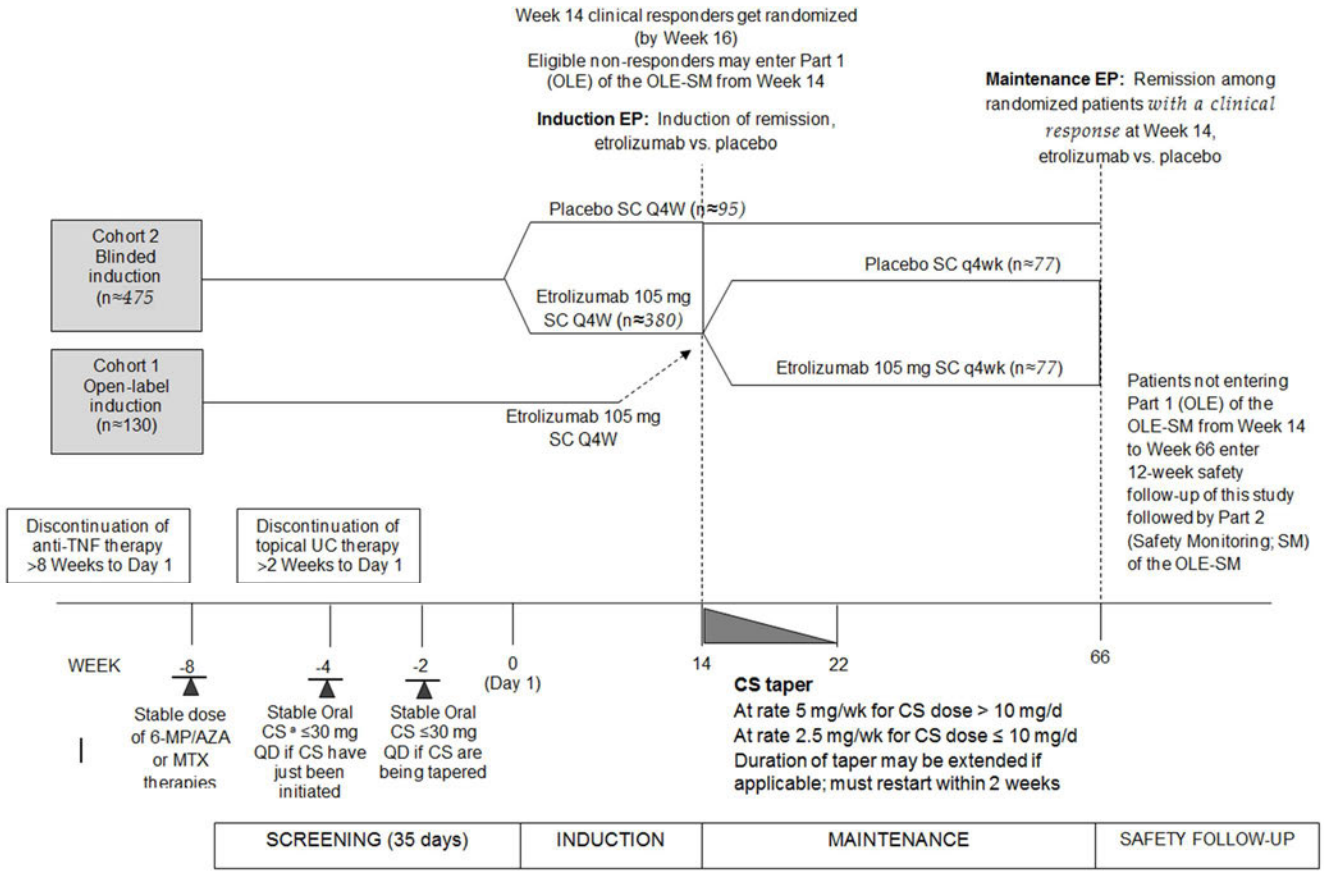
Endoscopy to document disease activity for patients exiting the treatment period early for any reason is strongly recommended.

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

At ANY time during the conduct of the trial, 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), anti-adhesion molecules, *Janus kinase (JAK) inhibitors,* cyclosporine, tacrolimus, or investigational agents are 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.

A complete list of study visits and assessments can be found in the Schedule of Assessments (see Appendix 1). Eligibility criteria for the transfer of patients to Study GA28951 and 12-week safety follow-up can be found in Table 4.

Figure 1 Study Schema



6-MP = 6-mercaptopurine; AZA = azathioprine; CS = corticosteroid; EP = endpoint; IS = immunosuppressant; MTX = methotrexate; OLE-SM = open-label extension–safety monitoring study (Study GA28951); Q4W = every 4 weeks; QD = once a day; QOD = every other day; SC = subcutaneous; wk = week.

[a] Stable budesonide at ≤ 9 mg/day. Taper from Week 14 to QOD for 2 weeks and then discontinue.

Number of Patients

A total of approximately 605 patients will be enrolled from approximately 225 sites via an open-label induction arm (Cohort 1, n = 130) and a double-blind induction arm (Cohort 2, n = 475).

Cohort 2 patients will be randomized in a 4:1 ratio to etrolizumab 105 mg SC (n ≈ 380) or placebo (n ≈ 95) Q4W. Patients in the etrolizumab arm of Cohort 2 who achieved a clinical response at Week 14 (see Table 1 for definition of clinical response) and all Week 14 clinical responders in Cohort 1 will be randomized into the Maintenance Phase and will receive either etrolizumab (105 mg SC Q4W) or placebo in a 1:1 ratio. It is estimated that the planned approximately 510 etrolizumab patients from Cohort 1 and Cohort 2 will provide approximately 154 patients in clinical response for randomization into the Maintenance Phase. Additional patients may be enrolled into Cohort 1, if needed, to meet sample size requirements for the Maintenance Phase.

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 risk-benefit 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 trial 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 66 weeks. Patients who do not achieve a clinical response at Week 14, patients who have clinical relapse during the Maintenance Phase, patients who receive defined rescue treatment (see Section 4.3.2.2), and patients who complete 66 weeks of the study may be given the option of enrolling into 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 study and then be requested to enroll in Part 2 (SM) of Study GA28951 for 92 weeks of monitoring for PML.

The total length of the study is expected to last from the first patient screened to either the last patient in last follow-up visit in this protocol or last patient enrolled into the Study GA28951 (OLE-SM), whichever is the 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 transferred to Study GA28951 (OLE-SM), 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 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 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 $C_{trough,ss}$ > 1.7 μg/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 in patients with moderately to severely active UC refractory to or intolerant of conventional and/or TNF inhibitor therapies. Results from this trial showed that at Week 10, the proportions of patients in clinical remission (defined as MCS $\leq$2 and all subscores $\leq$1) in the overall population (both TNF-naive and TNF-IR) were 20.5% in the 100-mg arms compared with 0% in the placebo arm. Data from SPRUCE (the OLE study) suggests that with longer duration of treatment, gut-selective anti-trafficking agents do benefit this patient population over time (Feagan et al. 2012). With 4 additional weeks of follow-up in OLE, clinically meaningful benefit was observed:

- 31% (10 of 32) of TNF-IR patients who had not responded to etrolizumab by Week 10 and rolled into the OLE achieved clinical response by pMCS at 14 weeks
- 9% (3 of 32) of TNF-IR patients who had not responded to etrolizumab by Week 10 and rolled into the OLE achieved clinical remission by pMCS at 14 weeks

In summary, because of the limitations of the currently available therapies for the treatment of moderately to severely active UC and the favorable benefit-risk observed in EUCALYPTUS, this Phase III trial is designed to test the efficacy and safety of etrolizumab in this patient population.

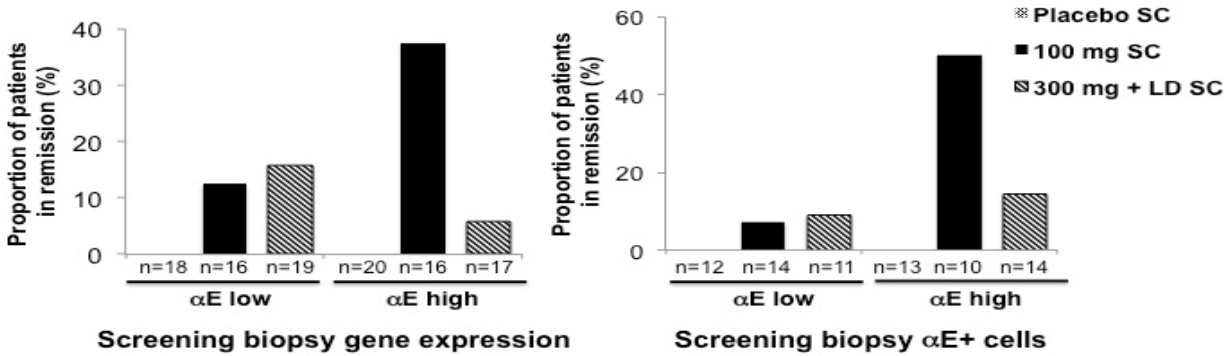
3.3.3 Rationale for Control Group

A placebo-treated control group will be used in this study to assess the differences in efficacy, safety, and tolerability in patients who receive etrolizumab plus background UC therapy compared with patients who receive placebo plus background UC therapy. The use of a control group is necessary given the inherent variability in disease flares and the use of subjective assessments, such as the patient-reported outcomes (PROs). Patients in the control group will undergo the same study assessments as the etrolizumab-treated patients.

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 β7 integrin and blocks α4β7:MAdCAM and αEβ7: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-IR patient population.

Figure 2 Effects of High and Low Baseline Expression of the αE Biomarker in Colon on the Remission Status of Ulcerative Colitis Patients Treated with Etrolizumab in EUCALYPTUS (Observed Data)



LD = loading dose; SC = subcutaneous.

All patients enrolled in the current study will have mandatory colonic mucosal sampling at the screening visit to analyze the relationship of αE levels (and potentially other biomarkers) with response to treatment. In addition, samples will be collected at Weeks 14 and 66 for potential exploratory PD biomarker analyses that include, but are not limited to, αE expression.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

Primary Efficacy Outcome Measures

Induction Phase

- Remission at Week 14, *as determined by the MCS*

Maintenance Phase

- Remission at Week 66 *among patients with a clinical response at Week 14, as determined by the MCS*

Secondary Efficacy Outcome Measures

Induction Phase

- Clinical remission at Week 14
- Clinical response at Week 14
- Improvement in endoscopic appearance of the mucosa at Week 14
- Endoscopic remission at Week 14
- *Histologic remission at Week 14*
- *Change from baseline in rectal bleed subscore at Week 6*
- *Change from baseline in stool frequency subscore at Week 6*
- Change from baseline in UC bowel movement signs and symptoms as assessed by the UC-PRO/SS measure at Week 14
- Change from baseline in UC abdominal symptoms as assessed by the UC-PRO/SS measure at Week 14
- Change from baseline in patients' health-related QOL at Week 14 as assessed by the overall score of the IBDQ

Maintenance Phase

- Clinical remission at Week 66 among patients in clinical remission at Week 14
- Clinical remission at Week 66
- *Remission at Week 66 among patients in remission at Week 14*
- Improvement in endoscopic appearance of the mucosa at Week 66
- *Histologic remission at Week 66*

- Endoscopic remission at Week 66
- Corticosteroid-free clinical remission at Week 66 (off corticosteroid for at least 24 weeks prior to Week 66) in patients who were receiving corticosteroids at baseline
- Corticosteroid-free remission at Week 66 (off corticosteroid for at least 24 weeks prior to Week 66) in patients who were receiving corticosteroids at baseline
- Change from baseline in UC bowel movement signs and symptoms as assessed by the UC-PRO/SS measure at Week 66
- Change from baseline in UC abdominal symptoms as assessed by the UC-PRO/SS measure at Week 66
- Change from baseline in patients' health-related QOL at Week 66 as assessed by the overall score of the IBDQ

Exploratory Efficacy Outcome Measures

- *Clinical response at Week 66 among patients with a clinical response at Week 14*
- *Remission at Week 66 among patients in clinical remission at Week 14*
- Corticosteroid-free clinical remission at Week 66 (off corticosteroid for at least 12 weeks prior to Week 66) in patients who are receiving corticosteroids at baseline
- *Histologic disease activity change from baseline to Week 14 and Week 66*
- *Improvement in histologic and/or endoscopic disease activity*
- Change in health utilities, as assessed by the EQ-5D, from baseline to Week 14 and Week 14 to Week 66
- Frequency and duration of hospitalizations from Week 14 to Week 66
- *Response, remission and corticosteroid-free endpoints as determined by the mMCS*

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
- Incidence and severity of hypersensitivity reaction events

3.4.3 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Serum trough concentration at steady-state during the dosing period from Week 16 to Week 66
- Serum concentration at primary endpoint time (Week 14 and Week 66)

3.4.4 Exploratory Biomarker Outcome Measures

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

- Remission at Week 14 and maintenance of remission at Week 66 in patients according to baseline levels of colonic tissue biomarkers and/or peripheral blood, including, but not limited to, αE integrin
- Changes in levels of exploratory colonic tissue and/or peripheral blood biomarkers during the Induction and Maintenance Phases
- 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

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population is 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 4.6.1.4, a rectal bleeding subscore ≥1, a stool frequency subscore of ≥ 1, and colonic involvement extending a minimum of 20 cm from the anal verge) and who have been previously exposed to TNF inhibitors.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Treatment within 5 years prior to screening with **one or two** induction regimens that contain TNF inhibitors (including TNF inhibitor biosimilars), as defined below:
  - Infliximab: 5 mg/kg IV, 2 doses
  - Adalimumab: 160 mg SC followed by an 80-mg dose
  - Golimumab: 200 mg SC followed by a 100-mg dose

    Patients will be categorized as TNF inhibitor refractory, TNF inhibitor intolerant, or neither refractory nor intolerant to TNF inhibitors. TNF inhibitor refractory and TNF inhibitor intolerant are defined as follows:

    TNF inhibitor refractory: Persistent signs and symptoms of active disease despite TNF inhibitor treatment or recurrence of symptoms during maintenance TNF inhibitor treatment (i.e., following prior clinical benefit)

    TNF inhibitor intolerant: History of intolerance to TNF inhibitors, (including, but not limited to, injection-site reactions, congestive heart failure, or infection)

- Able and willing to provide written informed consent
- 18–80 years of age, inclusive
- Diagnosis of UC established at least 3 months prior to 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 4.6.1.4, a rectal bleeding subscore ≥1, and a stool frequency subscore of ≥ 1 during the screening period (prior to Day 1). See Section 4.6.2.1 for additional information regarding the 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 Day 1. See Section 4.6.2.1 for additional information regarding the time window.
- Washout of TNF inhibitor therapy for at least 8 weeks preceding Day 1
- 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 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 Day 1. If corticosteroids are being tapered, the dose has to be stable for at least 2 weeks immediately prior to Day 1.

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

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

  May be receiving AZA, 6-MP, or MTX provided that the dose has been stable for at least 8 weeks immediately prior to 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 4).

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

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

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 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 4.6.1.4)

  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 corticosteroids within 30 days prior to screening with the exception of a single administration of IV corticosteroid
- Use of agents that deplete B or T cells (e.g., alemtuzumab or visilizumab) within 12 months prior to Day 1, except for AZA and 6-MP.
- Use of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) within 4 weeks prior to Day 1
- Chronic nonsteroidal anti-inflammatory drug (NSAID) use (Note: 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 $\leq$2 weeks prior to Day 1
- Apheresis (i.e., Adacolumn apheresis) within 2 weeks prior to 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 Day 1
- 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 $\geq$3 weeks prior to 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 co-morbidity, 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)
- Neurological 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 $\leq$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 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 HBV DNA test cannot be performed, the patient is not eligible for this study.

    If the HBV DNA test result 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 Day 1 or other intestinal pathogens (as assessed by stool culture and ova and parasite evaluation) within 30 days prior to Day 1
- Evidence of or treatment for clinically significant cytomegalovirus (CMV) colitis (based on the investigator's judgment) within 60 days prior to Day 1. Laboratory confirmation of CMV from colon biopsy 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 4.6.1.5)

  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) are not eligible for this study.

  Patients with a chest X-ray (posteroanterior [PA] and lateral) within 3 months of Day 1 suspicious for pulmonary TB are **not** eligible for this study.

- 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 Day 1

  Fungal infections of the nail beds

  Oral or vaginal candidiasis that has resolved with or without treatment prior to 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 Day 1
- History of organ transplant

Exclusion Criteria Related to Laboratory Abnormalities (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 into the Induction Phase through an interactive voice/Web–based response system (IxRS). After written informed consent has been obtained, all patients will receive a screening number, which will be assigned by the IxRS. Following completion of the screening period and after all patient eligibility requirements are confirmed, patients will be assigned an identification number (a different number from the screening number) on Day 1 and will receive open-label etrolizumab (Cohort 1; see Figure 3) or will be randomized to either placebo or etrolizumab (105 mg SC Q4W; Cohort 2). Randomization for Cohort 2 will be stratified by concomitant treatment with corticosteroids (yes/no), concomitant treatment with immunosuppressants (yes/no), and disease activity measured during screening (MCS ≤ 9/MCS ≥ 10). A permuted blocks randomization method will be used to obtain an approximately 1:4 ratio between the placebo and etrolizumab arms in Cohort 2.
At Week 16, following receipt of the endoscopy score, etrolizumab patients from either Cohort 1 or from Cohort 2 achieving a clinical response at Week 14 (see Table 1 for definition of clinical response) will undergo a second randomization, stratified by remission status at Week 14, concomitant treatment with corticosteroids (yes/no), disease activity measured during screening (MCS ≤ 9/MCS ≥ 10), and induction cohort (Cohort 1/Cohort 2), to either 105 mg etrolizumab SC or placebo in a 1:1 ratio (Maintenance Phase). In order to facilitate Maintenance Phase sensitivity analyses of outcomes for patients who achieved remission in the Induction Phase using alternative remission definitions (i.e., not including the Physician's Global Assessment [PGA] subscore of the MCS among remission criteria), the Week 14 remission status

stratification variable will consist of three levels according to whether remission was achieved with or without inclusion of the PGA criteria described in Table 1.

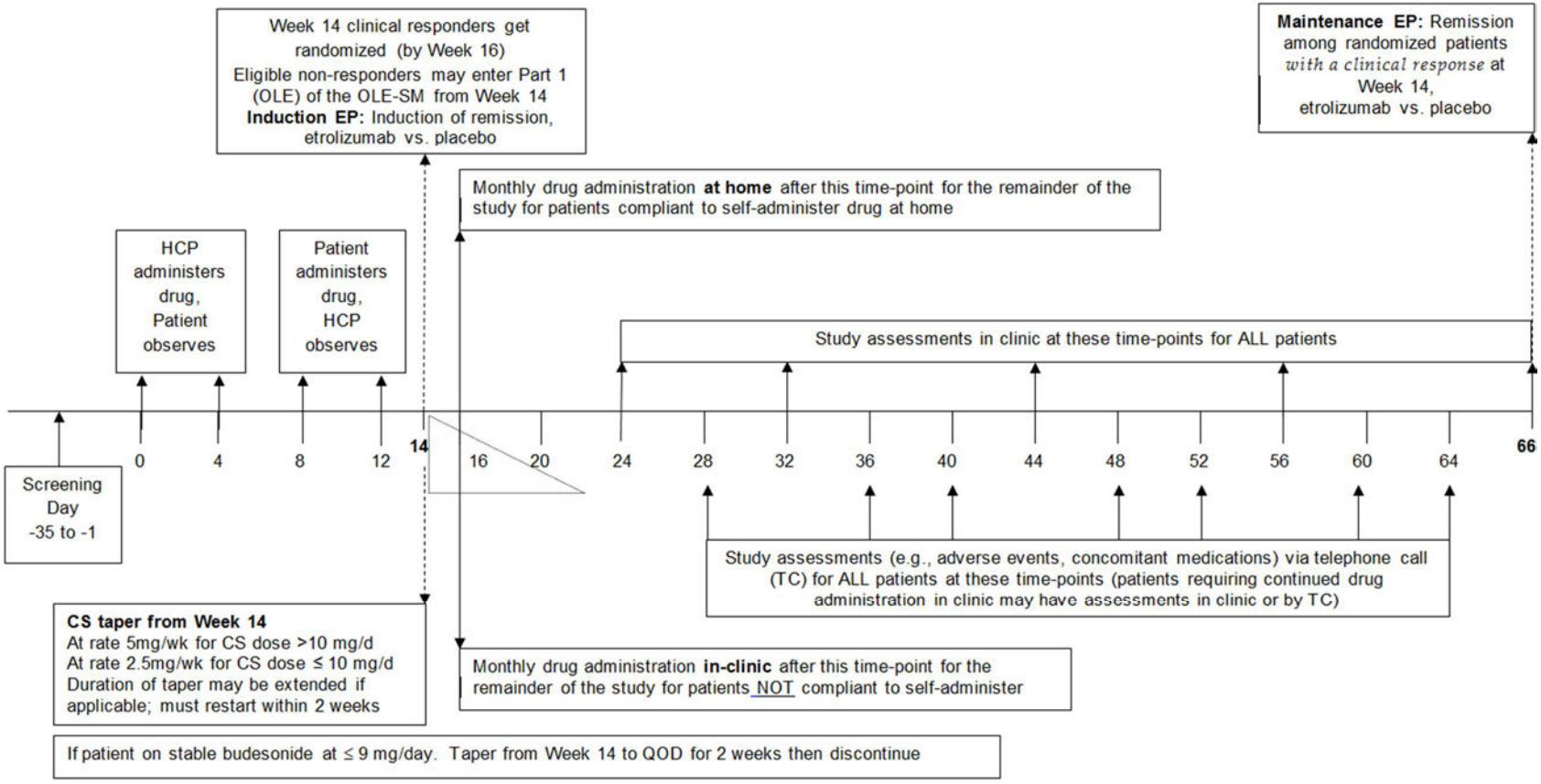
For the second randomization, a permuted blocks randomization method will be used to obtain an approximately 1:1 ratio between the treatment and placebo arm within each stratum. Study drug will be administered Q4W for a total of 13 doses with the final dose given at Week 64 (see Appendix 1 for details of study drug administration schedule). Patients achieving a clinical response while receiving placebo in the Induction Phase will continue on blinded placebo in the Maintenance Phase.

During the 14-week induction and 52-week maintenance double-blind treatment periods, the IxRS will make etrolizumab/etrolizumab placebo study treatment kit assignments. Each kit will consist of one prefilled 1-mL syringe (0.7 mL nominal volume). At each dosing visit (occurring every 4 weeks) during the blinded treatment period, one study drug kit will be assigned for administration to each patient. The placebo and active kits are filled and packaged to look identical. Patients performing study drug administration at home may receive 2 or 3 kits at a time beginning at Week 24 in order to allow sufficient supply until their next in-clinic visit.

Patients, all study site personnel, and the Sponsor and its agents will be blinded to treatment assignment throughout the 14-week double-blind (Cohort 2) induction and 52-week maintenance double-blind treatment periods. The IxRS service provider and personnel responsible for performing PK assays (in order to identify appropriate dilutions of PK samples to be analyzed) will be unblinded to patients' randomized treatment assignments. As described in Section 6, treatment assignment will be unblinded to the Sponsor personnel performing the analysis when all data through Week 66 are in the database and the data have been cleaned and verified. However, patients and all study site personnel will remain blinded to individual treatment assignment until after the study is completed (after all patients have either completed the 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; d = day; EP = endpoint; HCP = health care professional; OLE = open-label extension; OLE-SM = open-label extension–safety monitoring study; QOD = every other day; TC = telephone call; wk = week.

4.3 STUDY TREATMENT

Table 3 Treatment/Concomitant Background Treatments

	Treatment/Concomitant Background Treatment
Investigational medicinal product	Etrolizumab, 105 mg SC every 4 weeks Placebo SC every 4 weeks
Non-investigational medicinal products	
Induction Phase	Continuation of stable baseline doses of the following: 5-ASA (oral); AZA; 6-MP; MTX Corticosteroids up to 30 mg/day of prednisone (or equivalent) Budesonide up to 9 mg/day
Maintenance Phase	Responders who enter the Maintenance Phase should continue immunosuppressants (AZA, 6-MP, MTX) at a stable dose unless dose reduction or discontinuation is required due to immunosuppressant-related toxicity. Generally accepted criteria for discontinuation of IS 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 IS due to toxicity remains at the discretion of the investigator. During 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. Patients receiving budesonide are to taper their dose starting from Week 14 from 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 ulcerative colitis or corticosteroid withdrawal, 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-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; IS = immunosuppressants; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; SC = subcutaneous.

Table 3 Treatment/Concomitant Background Treatments (cont.)

	Treatment/Concomitant Background Treatment
Throughout Study	Probiotics and oral 5-ASA may be continued at a stable dose throughout. 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. Antidiarrheals (e.g., loperamide, diphenoxylate with atropine) for control of chronic diarrhea are permitted.

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; IS = immunosuppressants; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; SC = subcutaneous.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Etrolizumab and Placebo

Etrolizumab

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.

Placebo

Drug product composition for the placebo is exactly the same as that of 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]

[redacted] In the home setting, patients should be instructed to contact the study site 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 Investigator's Brochure.

4.3.1.2 Concomitant Background Treatment for Ulcerative Colitis

For concomitant background treatment for UC see Table 3.

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

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Etrolizumab and Placebo

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 is to be used for caregiver and not patient administration of study treatment.

For the initial 4 dose administrations, study medication is to be administered under close supervision of the HCP in a setting where medications and resuscitation facilities are available. The first two treatments (each 0.7 mL delivered via PFS; Week 0 [Day 1] and Week 4) will be administered by the HCP and observed by the patient (and/or caregiver). The following two treatments (Week 8 and Week 12) will be administered by the patient (or caregiver) and observed by the HCP in the clinic setting. Following the first four study treatment administrations, patients will be monitored for acute hypersensitivity reactions for at least one hour after the end of the injection. Epinephrine must be readily available for immediate use if required to treat anaphylaxis. Adjunctive medications such as parenteral diphenhydramine and inhaled bronchodilators 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 PML monitoring in Part 2 (SM) of Study GA28951.

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

Following the first four study drug administrations (Weeks 0−12), and therefore, completion of this first 3-month period training 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. 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 and information regarding recognition of symptoms of PML.

If the HCP/patient cannot administer study medication on the scheduled dosing day, study medication is to be administered within a window of +3 days from the scheduled dosing date. If the patient experiences a minor illness (e.g., minor infection), 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 two 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 5.1.5) should be documented on the appropriate adverse event electronic Case Report Form (eCRF) page. Patients administering the 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 Sections 4.7 *and 5.1*.

4.3.2.2 Concomitant Background Treatment and Rescue Therapy

Patients entering the study may be refractory to, dependent on, or intolerant to corticosteroids as defined below:

- Corticosteroid refractory: persistent symptoms of active disease despite history of at least one 4-week induction regimen that included ≥30 mg prednisone (oral) daily (or equivalent) for at least 2 weeks or ≥30 mg/day of IV prednisone (or equivalent) for at least 1 week
- Corticosteroid dependent: two failed attempts to taper corticosteroids below 10 mg/day of oral prednisone (or equivalent)
- Corticosteroid intolerant: history of intolerance to corticosteroids (including, but not limited to, Cushing's Syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, or infection)

All patients are to be defined in the eCRF as refractory, dependent, or intolerant to corticosteroids, if appropriate.

In addition, patients entering the study may be refractory to or intolerant to immunosuppressants 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)
- Persistent signs and symptoms of active disease despite a 6-TG level of ≥230 pmol/8 $\times 10^8$ RBCs during at least one 12-week regimen of oral AZA or 6-MP at a stable or increasing dose
- History of intolerance to AZA, 6-MP, or MTX (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function tests abnormalities, lymphopenia, TPMT genetic mutation, or infection)

All patients are to be defined in the eCRF as refractory or intolerant to immunosuppressants, if appropriate.

Management of Concomitant Medications during the Study

During Induction Phase (prior to Week 14)

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

During Maintenance Phase (after Week 14)

Corticosteroids

Corticosteroids are to be tapered starting from Week 14 in patients who achieve a clinical response (patients not achieving clinical response will be allowed to enroll in Part 1 (OLE) of Study GA28951. 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 $\leq$ 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 corticosteroid withdrawal, corticosteroid dose may be increased (up to the dose at study entry, if required), but tapering must begin again within 2 weeks.

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 due to 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

Induction Phase

In the Induction Phase, any patient who requires initiation of an immunosuppressant (AZA, 6-MP, or MTX), oral or topical 5-ASA, or corticosteroid, or increase in dose over baseline levels for treatment of worsening disease symptoms should stay in the study until Week 14, at which time he or she should enroll in Part 1 (OLE) of Study GA28951 to receive open-label etrolizumab, if eligible, or enter the 12-week safety follow-up. These patients may not continue into the Maintenance Phase of the study.

Maintenance Phase (after Week 14)

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.

Use of topical or IV corticosteroids or topical 5-ASA should also be avoided as concomitant medications. However, if these are clinically required to treat symptoms of UC, then the patient may remain in this 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. Patients who leave the treatment period early to enroll in Part 1 (OLE) of Study GA28951 should complete the early withdrawal from treatment visit prior to enrollment in Study GA28951.

Patients who were not receiving corticosteroids at baseline and patients who have completed the corticosteroid taper who subsequently 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 corticosteroid withdrawal may remain in this 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. Patients who leave the treatment period early to enroll in Part 1 (OLE) of Study GA28951 should complete the early withdrawal from treatment visit prior to enrollment in Study GA28951.

Endoscopy to document disease activity for all patients exiting the treatment period early is strongly recommended.

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 because of 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. However, patients who do initiate or escalate immunosuppressant therapy may remain in this blinded phase of the study or be given the option to enroll in Part 1 (OLE) Study GA28951, if eligible, based on the investigator's discretion. Patients who leave the treatment period early to enroll in Part 1 (OLE) of Study GA28951 should complete the early withdrawal from treatment visit prior to enrollment in Study GA28951. Endoscopy to document disease activity for patients exiting the treatment period early for any reason is strongly recommended.

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

At ANY time during the conduct of the trial, 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. 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 also be requested to enroll in Part 2 (SM) of Study GA28951 for 92 weeks of extended PML monitoring.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study, namely, etrolizumab and etrolizumab placebo, will be provided by the Sponsor. The investigator is responsible for the control of the drugs under investigation. The

investigational site will acknowledge receipt of IMP (e.g., drug receipt record) and disposition (e.g., drug dispensing log). Accountability will be assessed by maintaining adequate drug dispensing and return records. IxRS will be used to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

These records must contain the following:

- Documentation of drug shipments received from the Sponsor (date received and quantity)
- Disposition of unused study drug not dispensed to patients
- Drug Dispensing Log must be kept current and should contain the following information:

    Identification of the patient to whom the study medication was dispensed

    Date(s) and quantity of the study medication dispensed to the patient

    Date(s) and quantity of the unused study medication returned by the patient

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

4.3.4 Assessment of Compliance

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

Home-injection: An e-diary will be provided to patients to record home injections.

Patients will be asked to return all unused 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. Patients should also bring their e-diary to the clinic during visit.

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

A Drug Dispensing Log must be kept as described in Section 4.3.3. The investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator. When the study is completed, the investigator will return all completed Drug Dispensing Logs to the Monitors.

Any unused study drug and Drug Return Records should be returned to the Monitor, unless alternate destruction has been authorized by Roche or required by local or

institutional regulations (Section 4.3.3). The investigator's copy of the Drug Return Record(s) must accurately document the return of all study drug supplies to Sponsor.

4.3.5 Destruction of the Investigational Medicinal Product/Comparator

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

- Identity (batch numbers or subject numbers) of IMP(s) destroyed
- Quantity of IMP(s) destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person who destroyed investigational product(s).

In case of device failure or if there are any issues with the drug, the PFS should not be destroyed and instead should be returned to the investigator site in the packaging provided for this purpose. The device is to be sent from the investigator site to the appropriate Roche clinical trial supplies department for further assessment (see Section 4.3.6).

4.3.6 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, the device complaint must be reported on the PD103 IMP Deviation Form and the adverse event must be reported as a spontaneous adverse event to the Sponsor via telephone.

4.4 CONCOMITANT THERAPY

4.4.1 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 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 4.3.2.2.

4.4.2 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 AZA and 6-MP
- Use of cyclosporine, tacrolimus, sirolimus, or MMF
- Use of natalizumab, vedolizumab, efalizumab, or rituximab
- Use of TNF inhibitors (including TNF inhibitor biosimilars)
- Use of anti-adhesion molecules
- *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 entered into safety follow-up within this study.

4.5 CLINICAL RELAPSE

4.5.1 Definition of Clinical Relapse

Clinical relapse is defined as an:

- Increase in pMCS ≥ 3 points compared to induction timepoint (Week 14) AND absolute pMCS ≥ 5 AND endoscopic subscore ≥ 2

If a patient meets criteria for clinical relapse during the Maintenance Phase of the study, he or she may withdraw from this study and enroll in Part 1 (OLE) of Study GA28951 for open-label etrolizumab treatment, if eligible.

4.6 STUDY ASSESSMENTS

4.6.1 Description of Study Assessments

4.6.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases, procedures, and all medication taken in the 8 weeks prior to Day 1 (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies). A detailed history of medication used for UC is required for the 5 years prior to screening. Patients will be categorized as TNF inhibitor refractory, TNF inhibitor intolerant, or neither refractory nor intolerant to TNF inhibitors at screening (see definitions in Section 4.1.1).

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

4.6.1.2 Physical Examinations

A complete physical examination should include the evaluation of head, eye, ear, nose, and throat, and cardiovascular, dermatological, musculoskeletal, respiratory, GI, and neurological 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.

4.6.1.3 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 the indicated timepoints in Schedule of Assessments (see Appendix 1).

4.6.1.4 Ulcerative Colitis Disease Activity Assessments

Extent and duration of patient's disease are 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 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 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 4.6.2.1).

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 from treatment visit and any unscheduled visit(s) 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 3. Appendix 3 also outlines procedures to follow in the event of e-diary malfunction or loss.

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 during screening 4–16 days prior to Day 1.

Endoscopy will be also performed at Weeks 14 and 66 and/or withdrawal from study (early withdrawal from treatment visit, see Appendix 1).

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 the 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 a 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 and 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 UK sites ONLY, one of the latter pair of biopsies (2 samples) will be placed in storage solution at 4°C and shipped to the UK 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 lab 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 lab if necessary).
- If neither CMV testing or histopathologic confirmation of UC is needed, these additional 2 biopsy samples should not be obtained.

At Weeks 14 and 66 and/or at early withdrawal from treatment visit (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 and 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 (see Appendix 1). In UK sites ONLY, one of the latter pair of biopsies (2 samples) will be placed in storage solution at 4°C and shipped to the UK 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 patients will be educated regarding the signs and symptoms of PML. Close monitoring during the course of the study for any new symptoms or signs suggestive of PML will be performed, with regular neurologic examinations (including evaluation of cranial nerves, motor and sensory function, coordination, and mental status) as per the Schedule of Assessments (see Appendix 1). The PML Subjective Checklist (symptom assessment) and the PML Objective Checklist (neurologic evaluation) will be administered (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 5.2.3) (see Appendix 6 for the Algorithm for Evaluation of Progressive Multifocal Leukoencephalopathy [PML]). 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 only be resumed in patients where PML has been ruled out. See Appendix 6 for the Algorithm for Evaluation of Progressive Multifocal Leukoencephalopathy (PML).

After completing this 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 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 the Study GA28951 (OLE-SM) will consist of the PML assessment interview conducted by telephone at 6-month intervals.

4.6.1.5 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 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 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 differential 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 tests (sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatine phosphokinase, and uric acid)
- 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.
- C-reactive protein (CRP)
- C. difficile toxin assay in stool, stool culture and sensitivity testing, 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. 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

  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

- ATA assays

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

- JCV antibodies

  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.

- PK assays

  Serum samples will be collected for determination of etrolizumab concentrations in all patients during the Induction Phase and in all patients who were randomized into the Maintenance Phase. 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

- Exploratory diagnostic biomarker assays

  Peripheral blood, serum, stool, and colon biopsies will be assessed using qualified methods (including but not limited to ELISA, IHC, and/or qPCR) for exploratory and diagnostic biomarker analysis.

- *Histologic activity on colon biopsies using the Nancy histological index.*

- Exploratory PD biomarker assays

  Peripheral blood, serum, stool, and colon biopsies will be collected and qualified methods (including but not limited to ELISA, IHC, bacterial culture, and/or qPCR) will be utilized for exploratory PD biomarker analysis for samples that are assessed. 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 4.6.1.10), 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 for PK or 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 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.

4.6.1.6 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.

4.6.1.7 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 $\geq$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.

4.6.1.8 Patient-Reported Outcomes

Patient-reported outcomes (IBDQ, UC-PRO/SS, EQ-5D, and the stool frequency and rectal bleeding components of the MCS and pMCS) and physician-reported outcomes (PGA 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 other 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 UC-PRO/SS measure for at least 9–12 consecutive days around the time of each scheduled visit, as programmed in the e-diary.

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.

Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms (UC–PRO/SS) Measure

The UC-PRO/SS measure will be used to assess patient-reported UC signs and symptoms. The 14-item questionnaire (some questions contain supplementary questions regarding severity/frequency) contains three domains: bowel movement signs and symptoms, abdominal symptoms, and systemic symptoms. The UC-PRO/SS assesses the presence of UC symptoms and in some cases the severity or frequency of the symptoms. The UC-PRO/SS measure has a recall specification of 24 hours. A copy of the UC–PRO/SS measure is provided in Appendix 9.

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 10.

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 and as determined by the central reading procedure described in Section 4.6.1.4. 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 are provided in Appendix 3.

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 11.

4.6.1.9 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.

4.6.1.10 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 Informed Consent Form).

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).

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

Confidentiality

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

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

Patient medical information associated with RCR specimens is confidential and may only be disclosed to third parties 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 GA28950 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 GA28950.

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.

4.6.2 Timing of Study Assessments

4.6.2.1 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 enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening tests and evaluations will be performed within 35 days prior to Day 1 except for flexible sigmoidoscopy/colonoscopy which should be performed 4–16 days prior to 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 4.6.1.5). The ECG and chest X-ray can be obtained any time before Day 1 (see Section 4.6.1.6 and 4.6.1.7 for additional details on the chest X-ray and ECG). Colon biopsy specimen collection is detailed in Section 4.6.1.4.

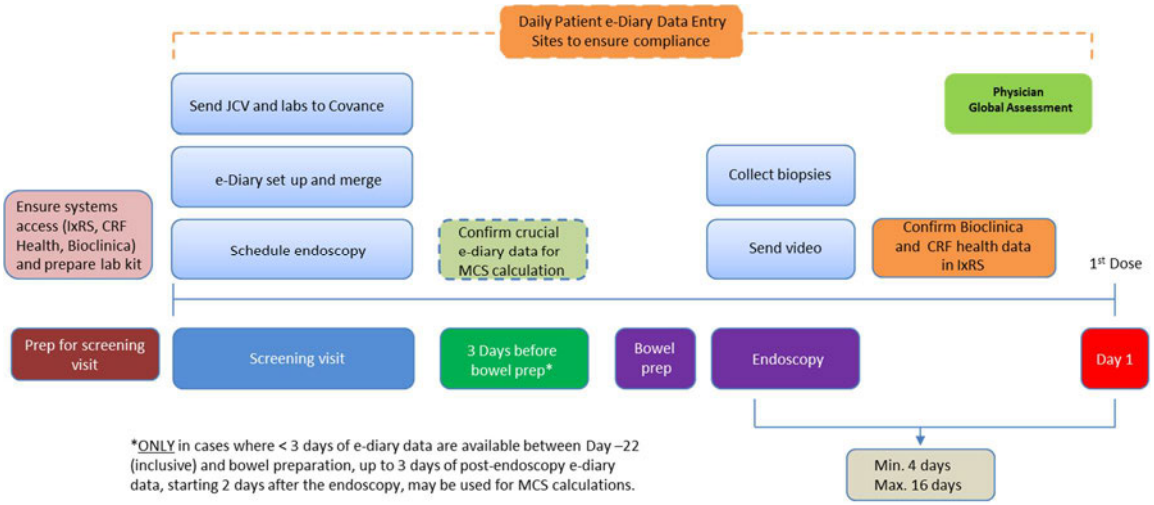
A blood sample to test for antibodies to JCV will be taken and stored for possible later assessment of how widespread the JCV infection is in the study population. Sample testing for the presence of JCV antibodies is not helpful in predicting risk for PML or for evaluating neurologic symptoms. The sample 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 Day 1 (i.e., Day –16 to Day –4; see Figure 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 4.6.1.4).

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 3.

The endoscopy and the 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 3.

Figure 4 Overview of Screening Activities



Note: Endoscopy should be performed 4–16 days prior to Day 1.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before 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.

4.6.2.1.1 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.

4.6.2.1.2 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 patients' 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 4.6.1.5, if a negative TB screening test result has been documented within 3 months before screening or rescreen, 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 Day 1 following the 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 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.

4.6.2.2 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 induction (Week 14) and maintenance (Week 66) 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 3).

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. Data will be collected as for a clinic visit at this time with the exception of blood sample and in clinic PRO assessments. All patients will be queried and closely monitored for any adverse event at all study assessment timepoints (every 4 weeks) during both clinic visits and study assessments made over the telephone. All adverse events and concomitant medications will be recorded and the patient questioned regarding a potential clinical relapse. An unscheduled visit is to be conducted as required (see Section 4.6.2.5).

All patients will receive hands-on training in 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.

4.6.2.3 Assessments at Study Completion/Early Withdrawal from Treatment Visit

The completion of the study treatment period is defined as the Week 66 visit. Patients who complete the treatment medication will be asked to visit the clinic for Week 66 assessments. Eligible patients who consent to receive open-label etrolizumab Part 1 (OLE) of Study GA28951 are to receive their first dose of open-label etrolizumab 4 weeks after their last dose of study medication in this study. On occasions where this first dose of etrolizumab in Part 1 (OLE) of Study GA28951 cannot be administered in accordance with these requirements, the first dose of etrolizumab is to be administered with a maximum delay of 2 weeks from the scheduled dosing day in Part 1 (OLE) Study GA28951.

If a patient leaves the study prior to Week 66, an early withdrawal from treatment visit is to be conducted on his or her next scheduled visit, including for those patients who are enrolling in Study GA28951 (OLE-SM). Assessments are specified in the Schedule of Assessments in Appendix 1. Following completion of assessments at this early withdrawal from treatment visit, eligible patients are to receive their first dose of open-label etrolizumab in Part 1 (OLE) Study GA28951 weeks after their last dose of study medication in this study, with a maximum delay of 2 weeks from the scheduled dosing day in Study GA28951.

At any timepoint, patients who are not eligible or who choose not to enroll in Part 1 (OLE) of Study GA28951 are to 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.

Patients who were treated with prohibited medication are to have their early withdrawal from treatment visit at their next scheduled visit followed by the 12-week safety follow-up phase of this study (telephone call at Week 6 and clinic visit at Week 12; see Appendix 2). Patients are to then enroll in Part 2 (SM) of Study GA28951 for extended PML monitoring.

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

The Study GA28951 (OLE-SM) will be conducted under a separate protocol and eligible patients as described below (also see Table 4) will need to be willing and able to provide separate informed consent to enter this study.

Note: Patients who are not eligible or who do not wish to receive open-label etrolizumab 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:

- In the Induction Phase, any patient who requires initiation of an immunosuppressant (AZA, 6-MP, MTX), corticosteroid, or oral or topical 5-ASA, or increase in dose of these medications over baseline levels for treatment of worsening disease symptoms may enroll in Part 1 (OLE) of Study GA28951 after the Week 14 assessment, if eligible.
- Patients who do not achieve a clinical response at Week 14
- Patients who meet the criteria for relapse (see Section 4.5.1 for definition) at any time between Week 14 and Week 66
- Patients who were not receiving corticosteroids at baseline and patients who have completed the corticosteroid 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 corticosteroid withdrawal.
- Patients who use IV or topical corticosteroids, who use 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
- All remaining patients at end of Week 66

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

- Patients who discontinue study treatment prior to Week 14 or do not perform the Week 14 visit
- Patients who require rescue medications that are prohibited in conjunction with etrolizumab (see Section 4.3.2.2)
- Patients with severe hypersensitivity reactions (see Section 4.7.1.1), malignancies, specific de novo or reactivated serious viral infections, PML, or other life-threatening infections during the trial (see Table 5 and Sections 4.7.1.1 and 5.1.5)

Table 4 Eligibility for Enrollment into Part 1 (OLE) of Study GA28951 or Transfer to 12-Week Safety Follow-Up

Time Period	Rationale	May Enroll in Part 1 (OLE) if Eligible (from Week 14 onward)	Must Transfer to 12-Week Safety Follow-Up of this study
Day 1 to Week 14	Initiation of an immunosuppressant (AZA, 6-MP, MTX) oral or topical 5-ASA, or corticosteroid, or increase dose in these medications over baseline levels.	Yes (may enroll at the 14-week timepoint)	Yes (must transfer to SFU if they do not choose OLE)
Week 14	Did not achieve a clinical response at Week 14	Yes	Yes (must transfer to SFU if they do not choose OLE)
Week 14 to Week 66	Met criteria for clinical relapse (see Section 4.5.1) at any time between Week 14 and Week 66	Yes	Yes (must transfer to SFU if patient does not choose to receive study medication in Maintenance Phase or to participate in OLE)
Day 1 to Week 66	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 corticosteroid taper	Yes	
Day 1 to Week 66	Use of IV or topical corticosteroids or oral or topical 5-ASA, or increase in dose of oral 5-ASA over baseline level	Yes	
Week 66	End of treatment period (all patients remaining)	Yes	Yes (must transfer to SFU if they do not choose OLE)
Day 1 to Week 14	Discontinuation of study treatment prior to Week 14	No	Yes (transfer after dosing termination visit)
Day 1 to Week 66	Patients requiring rescue medications that are prohibited (see Section 4.3.2.2)	No	Yes (transfer after dosing termination visit)
Day 1 to Week 66	Occurrence of severe hypersensitivity reactions (see Section 4.3.2.1), malignancies, specific de novo or reactivated serious viral infections , PML or other life-threatening infections during the study (see Table 5 and Sections 4.7.1.1 and 5.1.5)	No	Yes (transfer after dosing termination visit)

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; IV = intravenous; MTX = methotrexate; OLE = open-label extension; OLE-SM = open-label extension—safety monitoring; SFU = safety follow-up.

4.6.2.4 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 4 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 phone 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 into 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 the 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 discontinue from the study prior to completion of the 12-week safety follow-up will be asked to return to the clinic within 30 days (±7 days) after the last dose of study drug or last scheduled visit for an early termination visit (Appendix 2).

See Appendix 1 for the schedule of assessments performed at the study completion/early withdrawal from treatment visit.

After the study completion, adverse events should be followed as outlined in Sections 5.5 and 5.6.

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

4.6.2.5 Assessments at Unscheduled Visits

An unscheduled visit may occur at any time during the study, (i.e., due to 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 relapse will undergo the following:

- Review of e-diary data
- Recording of concomitant medications and procedures
- Collection of adverse events and serious adverse events
- Clinical chemistry and 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 sample, if indicated

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

4.7 PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 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

4.7.1.1 Discontinuation from Study Drug

Patients must discontinue study drug 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 Table 5 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 as defined by colon biopsy samples should discontinue study medication, but may be considered to restart study treatment only after consultation with the Medical Monitor once the event has resolved and treatment with appropriate anti-viral medication has been completed.

  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 4.4.2)

Patients who discontinue study drug prematurely for the reasons listed above will be asked to return to the clinic for a study completion/early withdrawal from treatment visit (see Section 4.6.2.3) and will continue to undergo safety follow-up assessments for 12 weeks within this study. Patients should then enroll in Part 2 (SM) of Study GA28951 for 92 weeks of monitoring for PML (see Section 4.6.2.4). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced.

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

4.7.2 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.

5.1.2 Progressive Multifocal Leukoencephalopathy

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 which 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, given the observation of PML risk with natalizumab, the Sponsor will continue to conduct extensive risk-monitoring procedures during the Phase III trials.

5.1.2.1 Screening and Patient Selection

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. At study screening, patients with a history of demyelinating disease, PML, or clinically significant abnormalities noted on baseline neurologic examination will be excluded from the study. Patients who have received natalizumab, efalizumab, or rituximab will also be excluded.

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.

5.1.2.2 Monitoring and Management

Study site personnel and patient participants will be educated regarding the signs and symptoms of PML and provided with alert cards. Close monitoring during the course of the study for any new signs or symptoms 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 (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 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 MRI with and without contrast. If there remains any suspicion for PML, the PML adjudication committee may recommend performing a lumbar puncture with CSF analysis for JCV DNA by PCR. If JCV DNA is detected, the patient should be treated as a PML case and the patient should permanently discontinue study drug and enter safety follow-up. Dosing with study treatments can only be resumed in patients where PML has been ruled out. Refer to Appendix 6 for the Algorithm for Evaluation of Progressive Multifocal Leukoencephalopathy (PML).

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).

5.1.3 Monitoring for Other Serious Infections

Patients will also be monitored closely for other serious infections during the study (see Table 5 for details). Patients and investigators will 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.

5.1.4 Monitoring for Hypersensitivity Reactions

In addition, throughout the study, patients will be monitored closely for hypersensitivity reactions (see Table 5 for details). Patients should be instructed to recognize the symptoms of any anaphylactic, anaphylactoid, or hypersensitivity reaction, and to contact an HCP or seek immediate care in case of any such symptoms. Patients will be provided with alert cards to remind them and a caregiver or partner of the symptoms.

5.1.5 Management of Specific Adverse Events

Table 5 Guidelines for Managing Specific Adverse Events

Event	Action to Be Taken
Serious Infections	• Patients who experience a serious infection event (i.e., an infection that is a serious adverse event) should not receive further study drug until the event has completely resolved and treatment with anti-infective medications has been completed. • All efforts should be made to identify the infectious agent. • For those patients who recover from a serious infection, study medication may be restarted following consultation with the Medical Monitor. • Any patient who experiences a specific de novo or reactivated serious viral infection such as HBV, HCV, HIV, should immediately 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 • Patients who develop life-threatening infections during the study should discontinue study drug.
Signs and symptoms of possible PML	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, then the investigator is required to follow the process described in the PML algorithm (see Appendix 6). If PML is suspected, a neurology consultation should be promptly arranged. Based on this evaluation, brain magnetic resonance imaging and cerebral-spinal fluid JCV analysis may be performed (see Appendix 6). The following are signs and symptoms that may potentially indicate PML: • Alteration in mental status (cognitive changes, including confusion, difficulty concentrating, memory loss) and altered behavior (including personality changes) • Higher cortical dysfunction, including impaired comprehension and/or formulation of language (aphasia), loss of ability to recognize objects, persons, sounds, shapes, or smells (agnosia) • Visual changes, including loss of visual fields (homonymous hemianopsia), double vision (diplopia) • Motor deficits, including weakness (hemiparesis, monoparesis), seizures, (generalized or partial), difficulties with speech (dysarthria,) or swallowing (dysphagia)

Table 5 Guidelines for Managing Specific Adverse Events (cont.)

Event	Action to Be Taken
Signs and symptoms of possible PML (cont.)	• Sensory deficits, including sensory loss (paresthesia) • Coordination deficits, including difficulty walking and maintaining balance (ataxia), lack of voluntary coordination of limb movement (limb ataxia) If PML is suspected then all investigational treatment should be withheld in that patient and may only be restarted if it is confirmed that the patient does not have PML.
Vaccinations	For 4 weeks prior, during, and for 12 weeks after the last dose of study medication, patients should not receive live vaccines.
Malignancies	• 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. • If any dysplasias or abnormalities are noted that could be consistent with malignancy, an oncologist or appropriate specialist should be consulted and no further doses of investigational product should be administered until a thorough clinical evaluation has been completed. • Patients who develop a malignancy (with the exception of local and resected basal or squamous cell carcinoma of the skin), or who develop adenocarcinoma in situ, high-grade squamous intraepithelial lesions, or cervical intraepithelial neoplasia 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.
Hepatic effects	Liver toxicity has been reported with other class drugs that target α4 integrins (natalizumab) and $\alpha 4\beta 7$ integrins (vedolizumab). Therefore, this potential risk is being monitored in the etrolizumab studies. In nonclinical chronic toxicology studies, no abnormalities indicating liver toxicity with etrolizumab were observed; the risk in humans is currently unknown. • Patients with significant liver function test abnormalities should be excluded from the etrolizumab clinical studies. • 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.

Table 5 Guidelines for Managing Specific Adverse Events (cont.)

Event	Action to Be Taken
Hypersensitivity reactions	In completed Phase I/II clinical trials of etrolizumab, one serious adverse event of hypersensitivity (Grade 2) has been reported, no anaphylactic, anaphylactoid, or severe hypersensitivity reactions were observed; however, anaphylaxis and hypersensitivity reactions will be closely monitored during the study. • Patients with a history of moderate or severe allergic or anaphylactic/anaphylactoid reactions to chimeric, human, or humanized antibodies, fusion proteins, or murine proteins are excluded from study participation. • The first four injections will be administered in the clinic. After the first four injections, the patient must be monitored for 60 minutes after each injection. • Health care professionals administering the study medication in the clinic must be trained in the appropriate administration procedures and be able to recognize the symptoms associated with potential anaphylactic, anaphylactoid, or hypersensitivity reactions and should be familiar with Sampson's criteria for defining anaphylaxis (Sampson et al. 2006; see Appendix 8). • Investigators and HCPs should also be trained to accurately and appropriately report these events immediately to the Sponsor as adverse events of special interest and as serious adverse events, if appropriate (see Section 5.2). • Medicinal products for the treatment of hypersensitivity reactions (e.g., epinephrine, antihistamines, and glucocorticoids). Epinephrine must be readily available for immediate use if required to treat anaphylaxis. Adjunctive medications such as parenteral diphenhydramine and inhaled bronchodilators may be used IN ADDITION to epinephrine if necessary. Resuscitation equipment should also be available. Site personnel must be able to detect and treat such reactions. • If a patient has symptoms of anaphylaxis or severe hypersensitivity, the administration of etrolizumab must be discontinued permanently. • HCPs should also instruct patients how to recognize the symptoms of any anaphylactic, anaphylactoid, or hypersensitivity reaction and to contact a HCP or seek emergency care in case of any such symptoms. • Subsequent injections can be administered at home. The patient will be advised to seek emergency care in response to any potential symptom of hypersensitivity and will receive two alert cards to remind them and a caregiver or partner of the symptoms. Detailed information regarding anaphylactic, anaphylactoid, or hypersensitivity reactions that occur during the study will be collected, regardless of whether the events are serious (see Section 5.2.2) or non-serious (see Section 5.2.3).

Table 5 Guidelines for Managing Specific Adverse Events (cont.)

Event	Action to Be Taken
Local injection-site reactions	*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 ≤ 10%, all of which were of mild intensity.* In the clinic setting, patients will 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 patient leaves clinic.
Pregnancies	Patients who become pregnant should be withdrawn from study drug and followed-up for the duration of the pregnancy (see Section 5.4.3 for details).

CMV = cytomegalovirus; HBV = hepatitis B virus; HCP = health-care professional; HCV = hepatitis C virus; JCV = John Cunningham virus; PML = progressive multifocal leukoencephalopathy.

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 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)

All serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). A serious adverse event is any adverse event that meets any of the following criteria:

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

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)

- 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.

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 5.1.5 and Sampson's Criteria in Appendix 8)

  Neurological signs, symptoms, and AE 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 Table 5)

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 Section 5.4.4).

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 the OLE-SM study (Study GA28951), adverse event reporting should follow requirements of the OLE-SM study (Study GA28951).

If the patient does not enter the OLE-SM study (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 (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, induration/swelling at injection site) or symptoms (e.g., pain, pruritus at injection site) rather than a diagnosis of allergic reaction or injection-site reaction.

Other Adverse Events

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

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

5.3.5.2 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 × 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 Drug Administration

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

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

All adverse events associated with an overdose or errors in administration of study drug (e.g., dosing outside of the allowed window and injection without completion of full volume administration) should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.12 Patient-Reported Outcome Data

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

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

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.

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

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

5.4.3.2 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 last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a paper Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 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 4.3.6 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 trial-related procedures until a final outcome can be reported.

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

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

5.5.2 Sponsor Follow-Up

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

5.6 POST-STUDY ADVERSE EVENTS

For patients who enter the OLE-SM study (Study GA28951), adverse event reporting should follow the requirements for the OLE-SM study (Study GA28951).

Post-study, if the patient does not enter OLE-SM study (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 6.4 (Identified Risks and Adverse Drug Reactions [Reference Safety Information]).

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

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

All serious related (as assessed by the investigator and/or Sponsor) adverse events occurring in a patient administered etrolizumab **at any time** during the 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

For the purpose of statistical analyses, the Induction and Maintenance Phases will be treated as two independent studies. The analysis of the Induction Phase will formally evaluate the efficacy and safety of 105 mg etrolizumab SC Q4W versus placebo as an induction therapy.

The analysis of the Maintenance Phase will formally evaluate the efficacy and safety of 105 mg etrolizumab SC Q4W versus placebo as a maintenance therapy.

The analysis of data from the 66-week treatment period (Induction and Maintenance Phases) will be performed when all data from this period are in the database and data have been cleaned and verified.

Whereas Sponsor personnel will be unblinded to treatment assignment to perform the primary analyses, patients and study site personnel will remain blinded to individual treatment assignment (for Cohort 2 patients and those re-randomized into the Maintenance Phase) 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

The study sample size was selected so that sufficient patients are enrolled to evaluate the primary endpoints in the blinded Induction Phase and the Maintenance Phase respectively. Approximately *605* patients will be enrolled in the open-label induction arm (Cohort 1, n≈130) or the blinded induction cohort (Cohort 2, n≈*475*).

Cohort 2 patients will be randomized in a 4:1 ratio to etrolizumab (n≈*380*) or placebo (n≈*95*). This will provide *approximately 80*% power to detect a 10% difference in remission rates at Week 14 between the etrolizumab and placebo arms, under the assumption of a placebo remission rate of ≤5% and a two-sided χ^2 test at the 5% significance level.

The primary endpoint for the Maintenance Phase is Week 66 remission among patients *with a clinical response* at Week 14. *In total, it is estimated that approximately 154 etrolizumab patients will achieve clinical response at the end of the Induction Phase and therefore will be randomized in the Maintenance Phase, under the assumption of a Week 14 clinical response rate of approximately 30% in the pooled etrolizumab induction group.*

A sample size of 154 patients in the Maintenance Phase will provide >90% power to detect a 30% difference in remission rates between the two maintenance arms, under the assumption of a placebo Week 66 remission rate ≤*10*% and a Fisher exact test at the 5% significance level.

The planned approximately *510* etrolizumab patients from Cohort 1 and Cohort 2 would provide approximately *154* patients *with a clinical response* at Week 14, under the assumption of a Week 14 *clinical response* rate of at least *30*% in the pooled (Cohort 1 and Cohort 2) etrolizumab induction group. Additional patients may be enrolled into Cohort 1, if needed, to achieve this target number of approximately *154* patients randomized into the Maintenance Phase.

For the purpose of statistical analyses and sample size calculations, the Induction and Maintenance Phases will be treated as two independent studies, and as such no adjustment to alpha is required.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients randomized and re-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, duration of disease, and MCS and its subscores will be summarized for all randomized patients by treatment group by use of descriptive statistics for both the Induction and Maintenance Phases. Exposure to study drug (number of study treatments and duration of treatment) will be summarized by treatment arm.

6.4 EFFICACY ANALYSES

- Efficacy analyses for the Induction Phase will be performed using a modified intent-to-treat analysis set including all patients randomized in Cohort 2 who received at least one dose of study drug with patients grouped according to the treatment assigned at randomization.
- Efficacy analyses for the Maintenance Phase will be performed using a modified intent-to-treat analysis set including patients randomized in the Maintenance Phase with patients grouped according to the treatment assigned at randomization.

- To manage the overall type I error, the primary and secondary endpoints within the Induction and Maintenance Phases, respectively, will be tested sequentially. Within each of the Induction and Maintenance Phases, respectively, the primary endpoint will be tested first at a two-sided 5% significance level. A small number of secondary endpoints will then be tested, sequentially, conditional on positive results for the corresponding primary endpoint and any preceding secondary endpoints. The remaining secondary endpoints and all exploratory endpoints will be considered to provide supportive information and no adjustments for multiple comparisons will be performed. All endpoints will be assessed at a nominal two-sided 5% significance level.

Patients who are non-evaluable for efficacy at a specific timepoint (e.g., due to missing data or transfer to Part 1 [OLE] of the OLE-SM protocol [Study GA28951]) will be considered non-responders for all response/remission type endpoints. In addition, for the Maintenance Phase, patients who initiated an agent not allowed in combination with etrolizumab (see Section 4.4.2), an immunosuppressant or corticosteroid (administered for the treatment of UC), or had an increase in dose over baseline levels for treatment of worsening disease symptoms will be considered non-responders thereafter. In the Induction Phase, initiation of an agent not allowed in combination with etrolizumab, an immunosuppressant, oral or topical 5-ASA, corticosteroid, or increase in dose over baseline levels will lead to non-responder classification.

For continuous outcomes (e.g., IBDQ, UC-PRO/SS), 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 herein and in Sections 6.4.1 and 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 pre-specified subgroups (e.g., based on age, sex, race/ethnicity, baseline UC medications, baseline CS dose).

Further details, including additional missing data handling rules, will be provided in the SAP.

6.4.1 Primary Efficacy Endpoint

In the Induction Phase, the proportion of patients from Cohort 2 in remission at Week 14 will be compared between the etrolizumab and placebo arms with use of the Cochran-Mantel-Haenszel test statistic stratified by the factors used at randomization: concomitant treatment with corticosteroids (yes/no), concomitant treatment with immunosuppressants (yes/no), and baseline disease activity (MCS $\leq$ 9/MCS $\geq$ 10).

The primary endpoint for the Maintenance Phase is Week 66 remission among patients *with a clinical response* at Week 14. *Patients who are randomized into the maintenance phase (i.e., clinical responders at Week 14) will be evaluated.* The difference in remission rates between the etrolizumab and placebo arms will be compared using the Cochran-Mantel-Haenszel test statistic stratified by induction cohort (1, 2), concomitant treatment with corticosteroids (yes/no), and baseline disease activity (MCS $\leq$ 9/MCS $\geq$ 10). The Fisher exact test will be used as a sensitivity analysis.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this Induction Phase are as follows:

- Proportion of patients in clinical remission at Week 14
- Proportion of patients with clinical response at Week 14
- Proportion of patients with improvement in endoscopic appearance of the mucosa at Week 14
- Proportion of patients in endoscopic remission at Week 14
- *Proportion of patients with histologic remission at Week 14*
- *Change from baseline in rectal bleed subscore at Week 6*
- *Change from baseline in stool frequency subscore at Week 6*
- Change from baseline to Week 14 in UC bowel movement signs and symptoms, as assessed by the UC-PRO/SS measure
- Change from baseline to Week 14 in UC abdominal symptoms, as assessed by the UC−PRO/SS measure
- Change from baseline to Week 14 in health-related QOL, as assessed by the overall IBDQ score

The secondary efficacy endpoints for the Maintenance Phase are as follows:

- Proportion of patients in clinical remission at Week 66 among patients in clinical remission at Week 14
- Proportion of patients in clinical remission at Week 66
- *Proportion of patients in remission at Week 66 among patients in remission at Week 14*
- Proportion of patients with improvement in endoscopic appearance of the mucosa at Week 66

- *Proportion of patients with histologic remission at Week 66*
- Proportion of patients in endoscopic remission at Week 66
- Proportion of patients in corticosteroid-free clinical remission at Week 66 (off corticosteroid for at least 24 weeks prior to Week 66) in patients who were receiving corticosteroids at baseline
- Proportion of patients in corticosteroid-free remission at Week 66 (off corticosteroid for at least 24 weeks prior to Week 66) in patients who were receiving corticosteroids at baseline
- Change from baseline to Week 66 in UC bowel movement signs and symptoms, as assessed by the UC-PRO/SS measure
- Change from baseline to Week 66 in UC abdominal symptoms, as assessed by the UC-PRO/SS measure
- Change from baseline to Week 66 in health-related QOL, as assessed by the overall IBDQ score

All the responder/remitter secondary endpoints will be analyzed in the same fashion as the primary endpoint. The continuous secondary endpoints will be analyzed using an analysis of covariance (ANCOVA) model with the factors used at randomization into the Induction/Maintenance Phases as stratification variables and the baseline value of the studied measure as a covariate. Baseline is defined here as the last available value prior to treatment in the Induction/Maintenance Phases.

Further details regarding the analysis of the secondary endpoints will be provided in the SAP.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows**:**

- *Proportion of patients with a clinical response at Week 66 among patients with a clinical response at Week 14*
- *Proportion of patients with remission at Week 66 among patients in clinical remission at Week 14*
- Proportion of patients with corticosteroid-free clinical remission at Week 66 (off corticosteroid for at least 12 weeks prior to Week 66) in patients who were receiving corticosteroids at baseline
- *Proportion of patients with change in histologic disease activity from baseline to Week 14 and Week 66*
- *Proportion of patients with improvement in histologic and/or endoscopic disease activity*
- Change in health utilities, as assessed by the EQ-5D, from baseline to Week 14

- Change in health utilities, as assessed by the EQ-5D, from Week 14 to Week 66
- Frequency and duration of hospitalizations from Week 14 to Week 66
- *Proportion of patients with response, remission and corticosteroid-free endpoints, as determined by the mMCS*

The analysis methods for the exploratory endpoints will be described in the SAP.

6.5 SAFETY ANALYSES

The safety analysis population for the Induction Phase will consist of all patients who received at least one dose of study drug during the Induction Phase with patients grouped according to the treatment actually received (open-label etrolizumab, blinded etrolizumab, or blinded placebo).

The safety analysis population for the Maintenance Phase will consist of all patients randomized into the Maintenance Phase with patients grouped according to the treatment actually received during the Maintenance Phase.

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

6.5.1 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.

6.5.2 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 at baseline and during the study will be tabulated by treatment arm.

6.6 PHARMACOKINETIC, PHARMACODYNAMIC, AND BIOMARKER ANALYSES

For PK assessment, group average serum-etrolizumab concentration versus time data will be tabulated and plotted. The serum pharmacokinetics of etrolizumab will be summarized with a mean serum concentration at steady state (trough) and at the two primary endpoint times (Weeks 14 and 66). 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.

PD and biomarkers analyses will include examination of changes over time in exploratory biomarkers post-treatment. Results will be summarized descriptively.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include but are not limited to hospital records,

clinical and office charts, laboratory notes, memoranda, 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, MRIs, ECGs, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

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

7.5 USE OF COMPUTERIZED SYSTEMS

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

7.6 RETENTION OF RECORDS

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. 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 trial is sponsored by F. Hoffmann–La Roche Ltd. Approximately *225* international study centers will participate in this study to enroll approximately *605* patients.

A contract research organization (CRO) will be contracted to manage the study and perform monitoring activities.

Centralized facilities (vendors) will be used to collect QOL data and endoscopy reading and interpretation; however, the investigator or a designee will also read the endoscopy if required for clinically indicated safety reasons.

A central laboratory (i.e., Roche or a vendor) will be used for most laboratory assessments, including histologic grading of colonic biopsies as per the laboratory manual. A selected group of assessments will be performed on site or by a local laboratory.

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

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

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Appendix 1
Schedule of Assessments

Assessments	Screening Day [a] – 35 to – 1	Treatment Period Study Week (± 3 days)																			Unscheduled Visit [d]	Early Withdrawal from Treatment Phase
		0 [b]	4	8	12	14	16	20	24	28 [c]	32	36 [c]	40 [c]	44	48 [c]	52 [c]	56	60 [c]	64 [c]	66		
Informed consent	x																					
Review eligibility criteria [e]	x	x																				
Demographic data	x																					
Pregnancy test [f]	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Vital signs (BP and pulse)	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
PML Neurologic Examination [i]	x		x			x			x		x			x			x			x	x [d]	x
Hematology	x	x				x			x					x						x	x [d]	x [j]
Chemistry	x	x				x			x					x						x	x [d]	x [j]
Urinalysis	x	x																			x [d]	
TB screen [k]	x																					
HIV test	x																					
Hepatitis B and C serology [l]	x																					

Appendix 1
Schedule of Assessments (cont.)

Assessments	Screening Day [a] – 35 to – 1	Treatment Period Study Week (± 3 days)																			Unscheduled Visit [d]	Early Withdrawal from Treatment Phase
		0 [b]	4	8	12	14	16	20	24	28 [c]	32	36 [c]	40 [c]	44	48 [c]	52 [c]	56	60 [c]	64 [c]	66		
Hepatitis B DNA [m]	x					x			x		x			x			x			x		
Hepatitis C RNA (Amplicor) [n]	x																					
PK sampling (serum) [o]		x				x			x					x						x	x [d]	x [j]
Anti-therapeutic antibody sample (serum) [o, p]		x	x			x			x					x						x [q]	x [d]	x [j, q]
Plasma sample [r] (storage for JCV antibody testing)	x																					
MCS (includes endoscopy) [s]	x [t]					x														x	x [d]	x [j]
Partial MCS (pMCS; excludes endoscopy) [u]		x [u]	x	x	x		x	x	x		x			x			x				x [d]	x [j]
Stool sample collection	x [v]	x [w]				x [w]														x [w]	x [d]	x [w]
Colonic biopsy (CMV if required)	x [x]																				x [d]	
Colonic biopsy (histopathological confirmation of UC if required)	x [y]																					
Colonic biopsies (formalin)	x [z]					x [aa]														x [aa]	x [d, aa]	x [j, aa]
Colonic biopsies (for qPCR)	x [z]					x [aa]														x [aa]	x [d, aa]	x [j ,aa]
Serum sample (CRP)		x				x														x	x [d]	x [j]
Serum sample (future exploratory PD) [o]		x				x			x					x						x		x
Blood sample (RNA Paxgene) [o, bb]		x				x			x											x		x

Appendix 1
Schedule of Assessments (cont.)

Assessments	Screening Day [a] – 35 to – 1	Treatment Period Study Week (± 3 days)																			Unscheduled Visit [d]	Early Withdrawal from Treatment Phase
		0 [b]	4	8	12	14	16	20	24	28 [c]	32	36 [c]	40 [c]	44	48 [c]	52 [c]	56	60 [c]	64 [c]	66		
Whole blood (EDTA Blood) optional		x																				
UC-PRO/SS [cc]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
IBDQ [dd]		x				x														x		
EQ-5D [dd]		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
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Initial randomization		x																				
Randomization of responders to Maintenance Phase						x [ee]																
Etrolizumab/etrolizumab placebo [ff]		x	x	x	x		x [ff]	x [ff]	x [ff]	x [ff]	x [ff]	x [ff]	x [ff]	x [ff]	x [ff]	x [ff]	x [ff]	x [ff]	x [ff]			

BP = blood pressure; CMV = cytomegalovirus; CRP = C-reactive protein; ECG = electrocardiogram; eCRF = electronic case report form; EQ-5D = EuroQoL Five-Dimension Questionnaire; HBV = hepatitis B virus; HCV = hepatitis C virus; IBDQ = Inflammatory Bowel Disease Questionnaire; IHC = immunohistochemistry; JCV = John Cunningham virus; MCS = Mayo Clinic Score; PD = pharmacodynamic; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy; qPCR = quantitative polymerase chain reaction; UC-PRO/SS = Ulcerative Colitis Patient-Reported Outcome Signs and Symptoms; TB = tuberculosis; UC = ulcerative colitis.

Appendix 1
Schedule of Assessments (cont.)

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.

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

[b] Day 1 of Week 0.

[c] 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.

[d] Unscheduled visit represents a visit that is not as per Schedule of Assessments and is required for an adverse event or for potential relapse assessment. All indicated assessments are NOT performed at each unscheduled visit. Assessments would be symptom-driven (e.g., perform PML neurological examination only if patient reports symptoms suspected of PML; and confirmation of clinical relapse is performed by the Mayo Clinic Score assessment). Assessments corresponding to items noted in this column should be recorded on the eCRF.

[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 are surgically sterile. Urine test at all other visits; if urine test result 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 result via e-diary. Patients must be instructed at screening and reminded throughout the study that in case of positive pregnancy test result 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.

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

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

[i] PML neurologic exam 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 and assessment 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; e.g., Mantoux test), INF-γ based test (e.g., QuantiFERON®-TB Gold).

[l] Patients must undergo screening for HBV and hepatitis C. 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 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] The PK, ATA, and exploratory PD sample collections will be from all patients during the Induction Phase. During the Maintenance Phase, PK, ATA, and exploratory PD samples will only be collected from patients who were randomized into the Maintenance Phase.

Appendix 1
Schedule of Assessments (cont.)

[p] If serum sickness or a clinically significant allergic drug reaction is suspected, Sponsor should be notified and serum for etrolizumab 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.

[q] 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).

[r] 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.

[s] Endoscopy + rectal bleeding assessment + stool frequency assessment + Physician's Global Assessment (PGA). Patients who have not undergone full colonoscopy with documented results within 1 year prior to screening should undergo colonoscopy in lieu of sigmoidoscopy at the screening visit to allow for screening for cancer/dysplasia (yes/no).

[t] Screening endoscopy (for the MCS) should be performed 4–16 days prior to Day 1 (i.e., Day –16 to Day –4). For baseline measurements, the PGA will be obtained only once, on Day 1 (prior to randomization), and the PGA subscore will be used to calculate both the baseline (screening) MCS and the baseline (Day 1) pMCS.

[u] Partial MCS during screening is defined as the MCS score excluding the endoscopy score (i.e., rectal bleeding assessment + stool frequency assessment + PGA).

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

[w] 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).

[x] 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 lab if necessary. Result must be negative for CMV prior to dosing on Day 1.

[y] 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.

[z] In addition to the optional biopsy noted in footnote "x" and "y" above, 5 pairs (10 biopsy samples) will be obtained at screening (all taken from the most inflamed area of the colon within 20-40 cm of the 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 a stabilization buffer (such as RNAlater or a similar buffer) and stored at –80°C (1 pair for diagnostic qPCR and 1 pair for PD biomarkers). In UK sites ONLY, one of the latter pair of biopsies (2 samples) will be placed in storage solution at 4°C and shipped to the UK laboratory. The other 3 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.

Appendix 1
Schedule of Assessments (cont.)

[aa] A total of four pairs (8 biopsy samples) will be obtained from all patients (all taken from the most inflamed area of the colon within 20-40 cm of anal verge [sigmoid]). All will be sent to the central laboratory for further storage or distribution. In UK sites ONLY, one of the latter pair of biopsies (2 samples) will be placed in storage solution at 4°C and shipped to the UK laboratory. 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. The other two 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.

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

[cc] 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), starting from the first screening visit, and for at least 9−12 consecutive days around the time of each scheduled visit for the UC-PRO/SS.

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

[ee] Randomization to occur within 2 weeks starting from Week 14 timepoint.

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

Appendix 2
12-Week Safety Follow-Up

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

ATA = anti-therapeutic antibody sample; 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 exam consists of the PML Subjective Checklist and the PML Objective Checklist. Administer before other assessments as per Appendix 5.

[e] At all timepoints indicated and whenever serum sickness is expected. ATA samples may be used for PK and/or exploratory PD assessments.

Appendix 3
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 3
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 patient's normal stool 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 (see Figure 1 below). 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 3
Mayo Clinic Score Measurement (cont.)

The post-baseline stool frequency value for endpoint assessment will be calculated as the average (rounded to the nearest integer) from the three most recent stool frequency scores that were entered in the e-diary 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.

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.

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 Day 1 (i.e., Day –16 to Day –4).

Appendix 3
Mayo Clinic Score Measurement (cont.)

4. Physician's Global Assessment

The Physician's Global Assessment (PGA) 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 PGA 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 and a rectal bleeding subscore ≥1, and a stool frequency subscore ≥ 1.

2. Achievement of Clinical Response at Week 14

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

3. Identification of Clinical Relapse

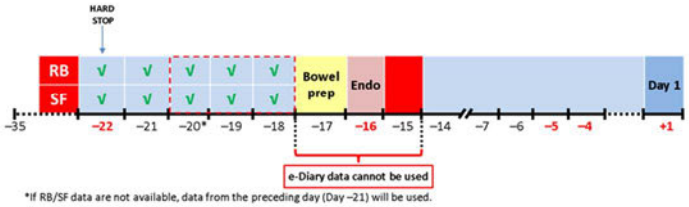
Clinical relapse is defined as an increase in pMCS ≥3 points compared with induction timepoint (Week 14) AND absolute pMCS of ≥5 AND an endoscopy subscore of ≥2

Appendix 3
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

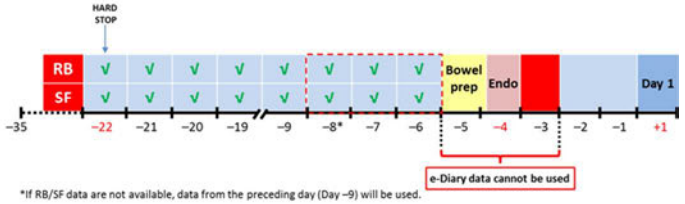
The e-diary data from the 3 consecutive days immediately preceding the bowel preparation day (Day –17 in this scenario) are used to derive RB and SF data for MCS calculation (Day –20 to Day –18, highlighted with red dashed lines in the figure). If e-diary data from these days are missing, RB/SF data 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

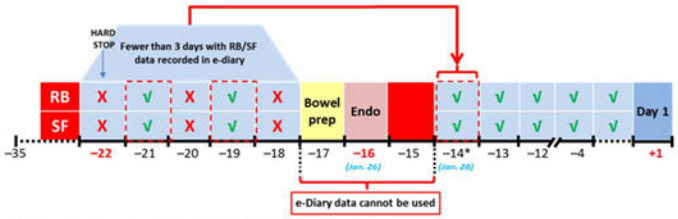
The e-diary data from the 3 consecutive days immediately preceding the bowel preparation day (Day –5 in this scenario) are used to derive RB and SF data for MCS calculation (Day –6 to Day –8, highlighted with red dashed lines in the figure). If e-diary data from these days are missing, RB/SF data from 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.



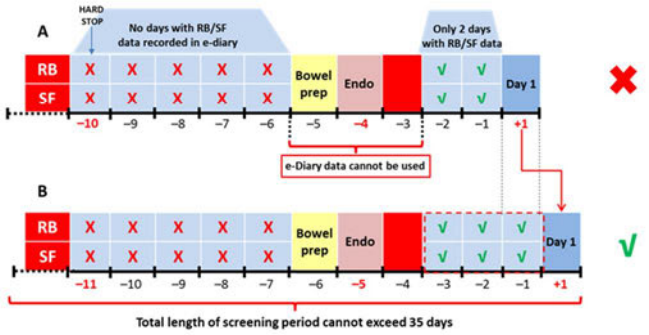
*If RB/SF data are not available, data from the next day (Day –13) will be used.

√ 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 3
Mayo Clinic Score Measurement (cont.)

Figure 1 Derivation of Stool Frequency and Rectal Bleeding Subscores at Screening (cont.)

Endo = endoscopy; MCS = Mayo Clinic Score; prep = preparation; 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.

Appendix 3
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 ≥ 3 points compared with induction timepoint AND absolute partial MCS ≥ 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 4
Childbearing Potential, Pregnancy Testing, and Contraception

All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening and a urine pregnancy test prior to administration of study drug at subsequent visits. If a urine pregnancy test result is positive, study drug will not be administered 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 post-menopausal (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 only acceptable 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 post-surgical verification of the absence of spermatozoa in the ejaculate
- Double barrier methods: condom **and** occlusive cap (diaphragm or cervical/vault caps) **with** spermicidal foam/gel/film/cream/suppository (Note: a female condom and male condom should not be used together as friction between the two can result in either product failing)

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

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

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

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

Appendix 5
Worksheet for the PML Neurologic Examination

PML SUBJECTIVE AND OBJECTIVE CHECKLISTS OF NEUROLOGIC ASSESSMENTS TO MONITOR FOR PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) IN THE ETROLIZUMAB PHASE III STUDIES

PML usually manifests with subacute, progressive neurologic deficits including:

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

In order to monitor patients for PML, a neurologic exam (including evaluation of cranial nerves, motor and sensory function, coordination, and mental status) will be performed as per the Schedules of Assessments (see Appendix 1 and Appendix 2). This neurologic exam will consist of administration of the PML Subjective Checklist and the PML Objective Checklist.

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

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

Appendix 5
Worksheet for the PML Neurologic Examination (cont.)

PML Subjective Checklist

Symptoms	"Compared to how you usually feel, have you had a significant change in any of the following?"		If the answer is "Yes", obtain a description of the symptom(s) with examples	Applicable Objective Test(s): Document result on PML Objective Checklist Worksheet
	YES	NO		
1. Have you been experiencing any persistent difficulty with your vision such as loss of vision or double vision? Have you been having trouble with reading?				• Test visual fields and ocular motility
2. Have you been experiencing any persistent difficulty speaking or having your speech understood by others?				• Casual observation of speech output for dysarthria or aphasia.
3. Have you been experiencing any persistent weakness in an arm or a leg?				• Test for pronator drift (Barre maneuver). • Assess gait. • Test muscle strength *(only if indicated).*
4. Have you noticed yourself regularly bumping into things or having difficulty writing?				• Observe tandem gait and finger to nose.
5. Have you regularly been experiencing difficulty understanding others?				• Test ability to follow serial commands.
6. Have you had persistent problems with your memory or thinking?				• Recall of 3 objects over 1 minute with distraction *(only if indicated).*
7. Have you been experiencing any persistent numbness or other loss of sensation?				• Test sensation side to side with either pinprick or cold *(only if indicated).*

Appendix 5
Worksheet for the PML Neurologic Examination (cont.)

PML Objective Checklist

Neurologic function being assessed	Instructions (bold text indicates parts of exam required at each visit, as specified in Schedule of Assessments)	Abnormal exam?		If the answer is "Yes", describe the abnormal objective exam finding
		YES	NO	
1. Visual fields and ocular motility	• **Visual Field Testing** • **Ocular Motility Testing**			
2. Speech	• **Observe the patient's speech output for dysarthria or aphasia.**			
3. Strength	• **Pronator drift test (Barre maneuver)** • **Gait testing (normal, heel and toe walk)** • *ONLY* if the patient has any subjective complaints of weakness, test muscle strength of the relevant			
4. Coordination	• **Observe tandem gait and finger to nose**			
5. Comprehension	• **Test ability to follow serial commands** • **"Take a piece of paper in your hand, fold it in half, and put it on the floor."**			
6. Memory and thinking	• *ONLY* if the patient has subjective complaints about their memory or thinking, test the ability of the patient to recall 3 objects over 1 minute with distraction			
7. Sensation	• *ONLY* if the patient has subjective sensory complaints, evaluate relevant areas based on patient's subjective complaints by comparing left vs. right side sensation to cold (e.g. alcohol swab or cold stethoscope) or pinprick (e.g. broken Q-tip)			

Appendix 5
Worksheet for the PML Neurologic Examination (cont.)

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

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

Please complete the PML eCRF.

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

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

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

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

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

Is PML suspected? (Yes/No)

Appendix 5
Worksheet for the PML Neurologic Examination (cont.)

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

1. Visual fields and ocular motility

Visual Field Testing:

- Position yourself approximately 3 feet away from the patient, with eyes at the same level.
- Keeping both eyes open, ask the patient to cover one eye and ask if all parts of your face and head are clear to them. Ask them to repeat, covering the other eye.
- Have the patient cover one eye and stare at your nose, and then ask them how many fingers you are holding up, testing each of the 4 visual quadrants. Repeat with the other eye covered.

Ocular Motility Testing:

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

2. Speech

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

3. Strength

Pronator drift test (Barre maneuver):

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

Appendix 5
Worksheet for the PML Neurologic Examination (cont.)

Gait testing:

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

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

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

Appendix 5
Worksheet for the PML Neurologic Examination (cont.)

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

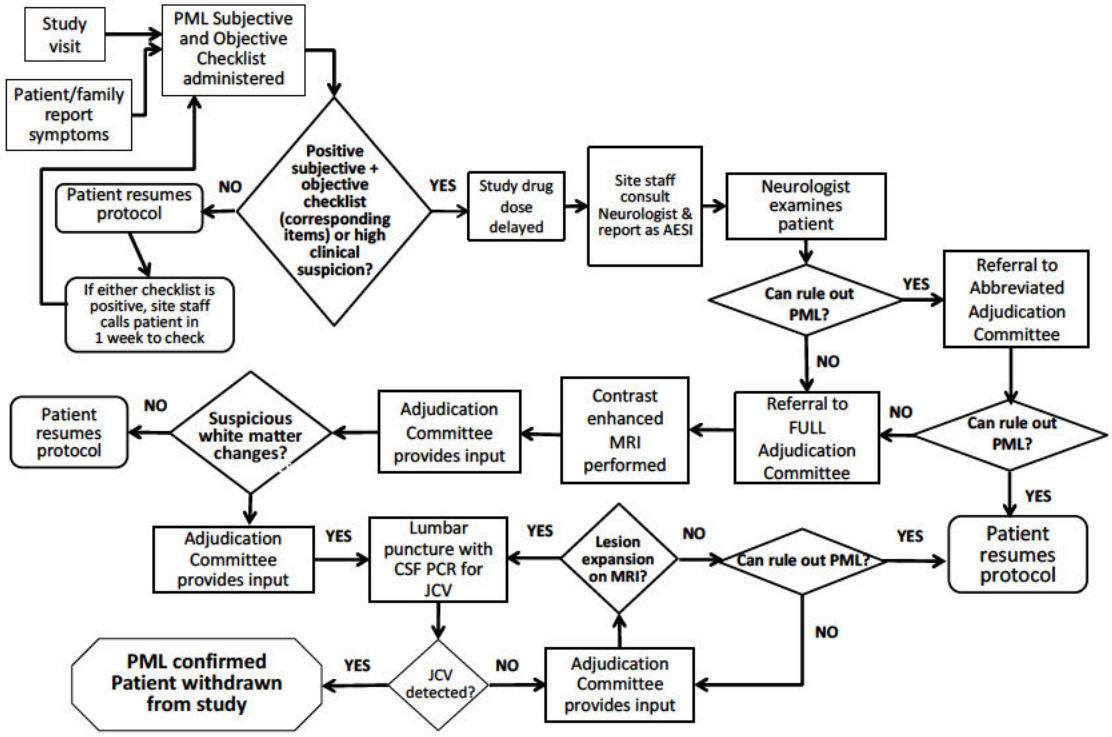
- *(ONLY* if the patient has subjective complaints about their memory or thinking) test the ability of the patient to recall 3 objects over 1 minute with distraction.

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 7
Patient Daily Diary (cont.)

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

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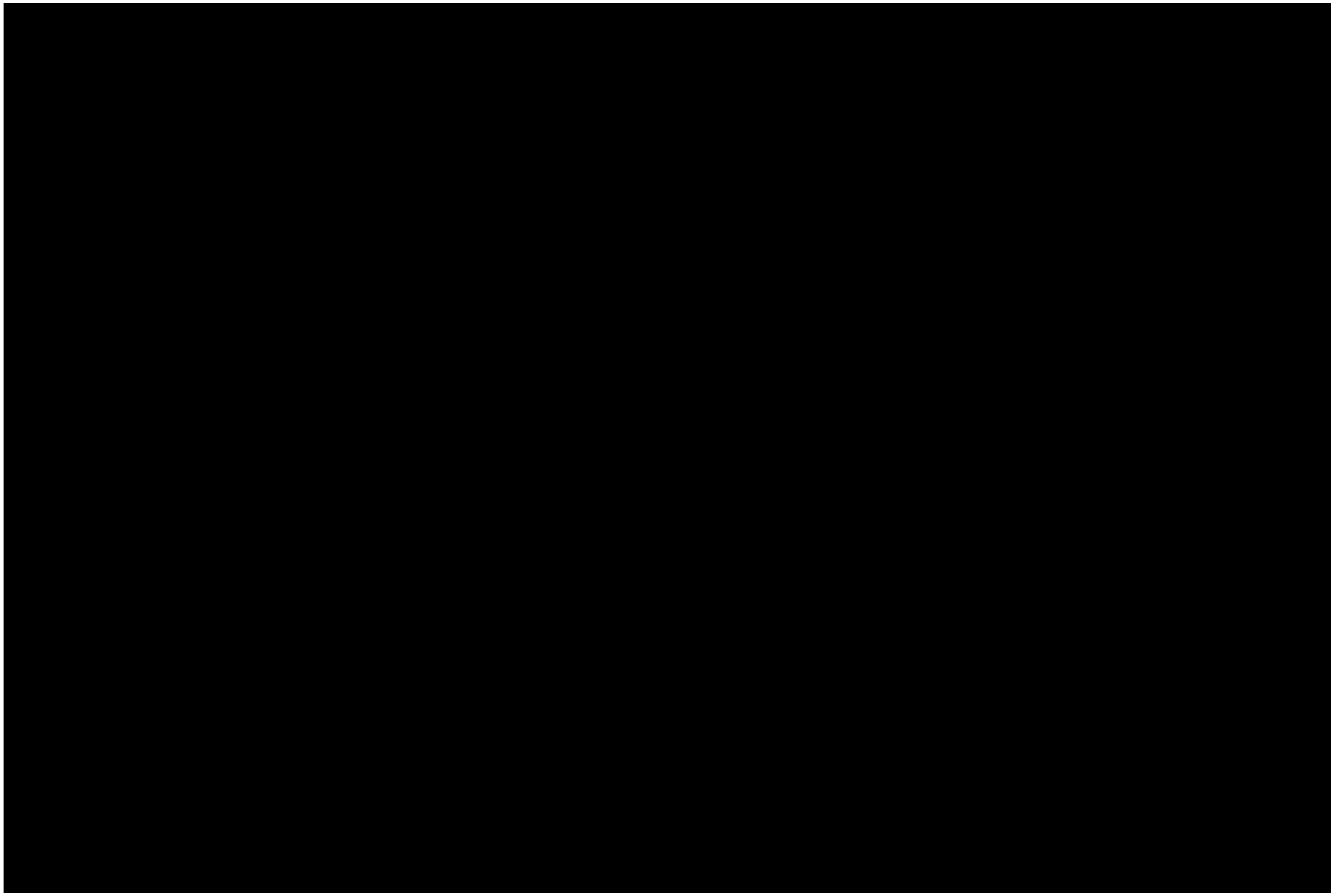
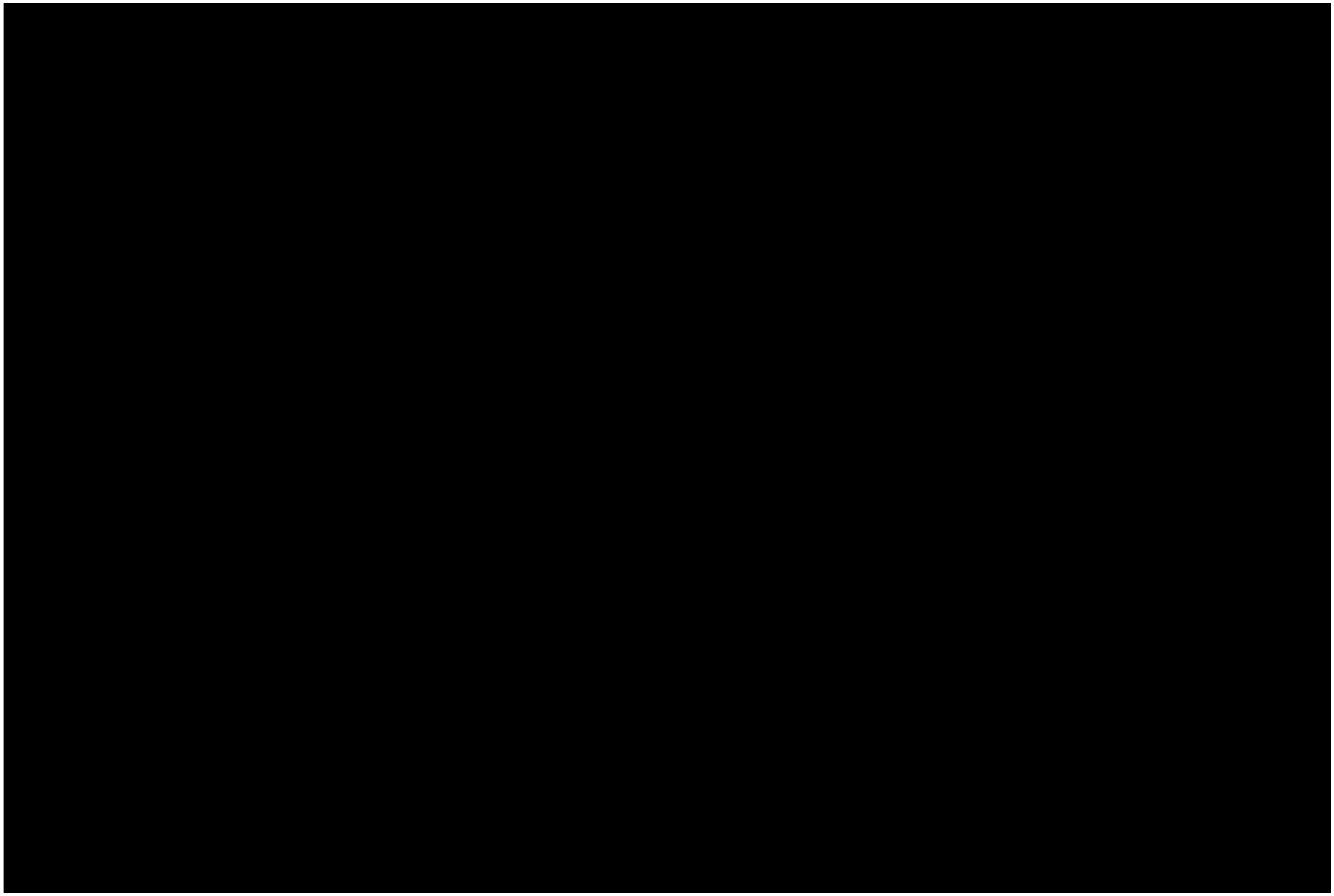
[1] Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–7.

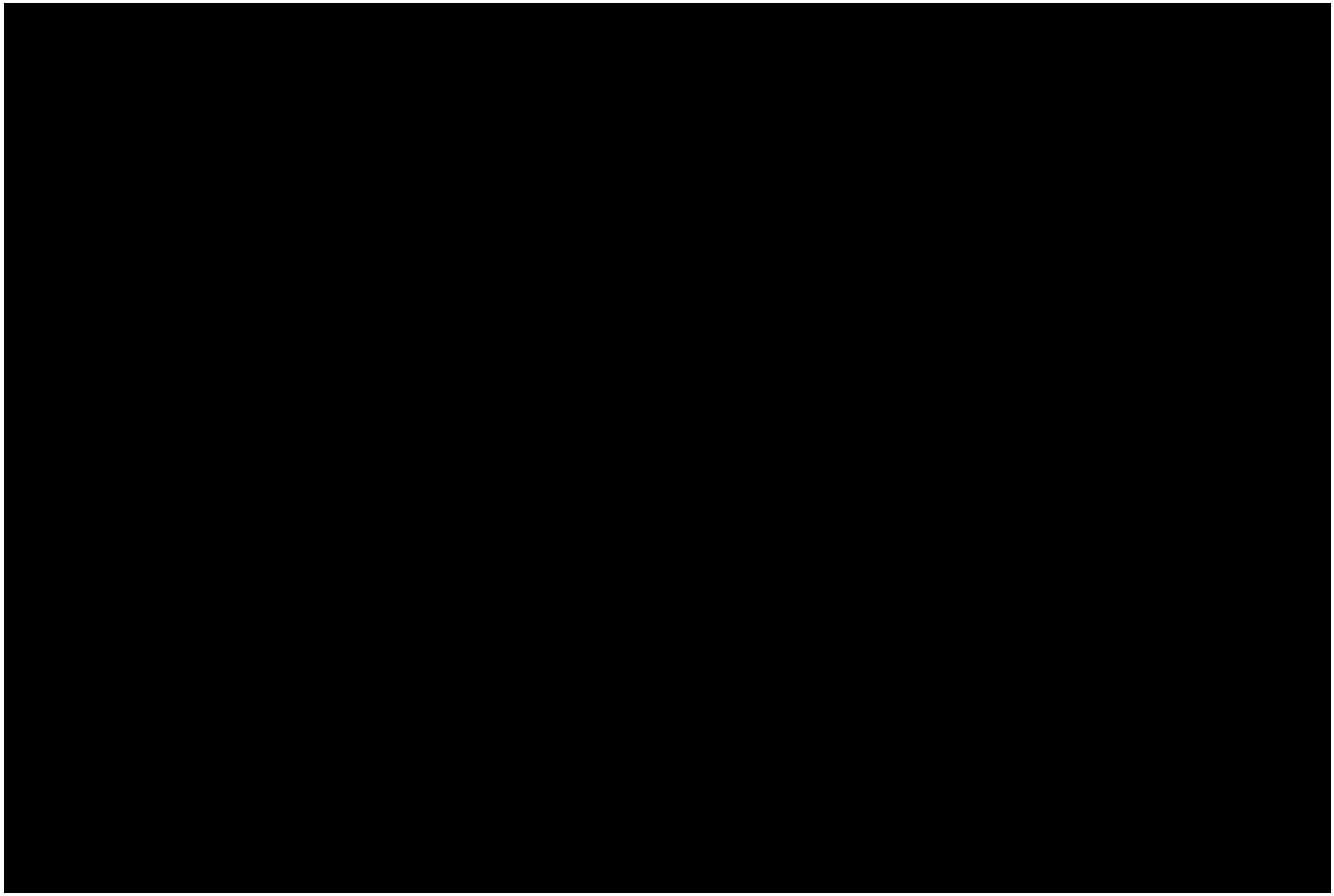
[2] Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 x age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.

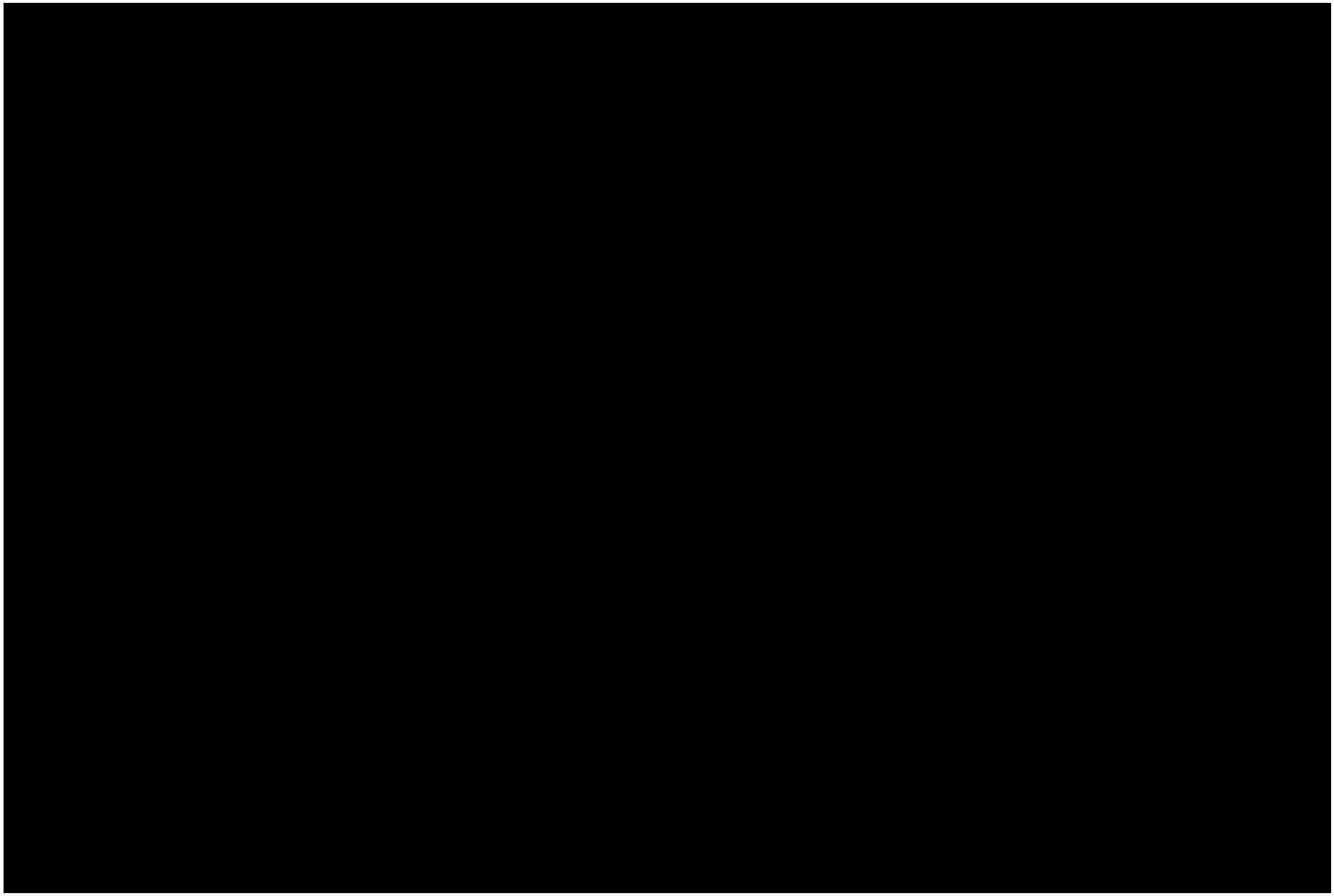
[redacted]

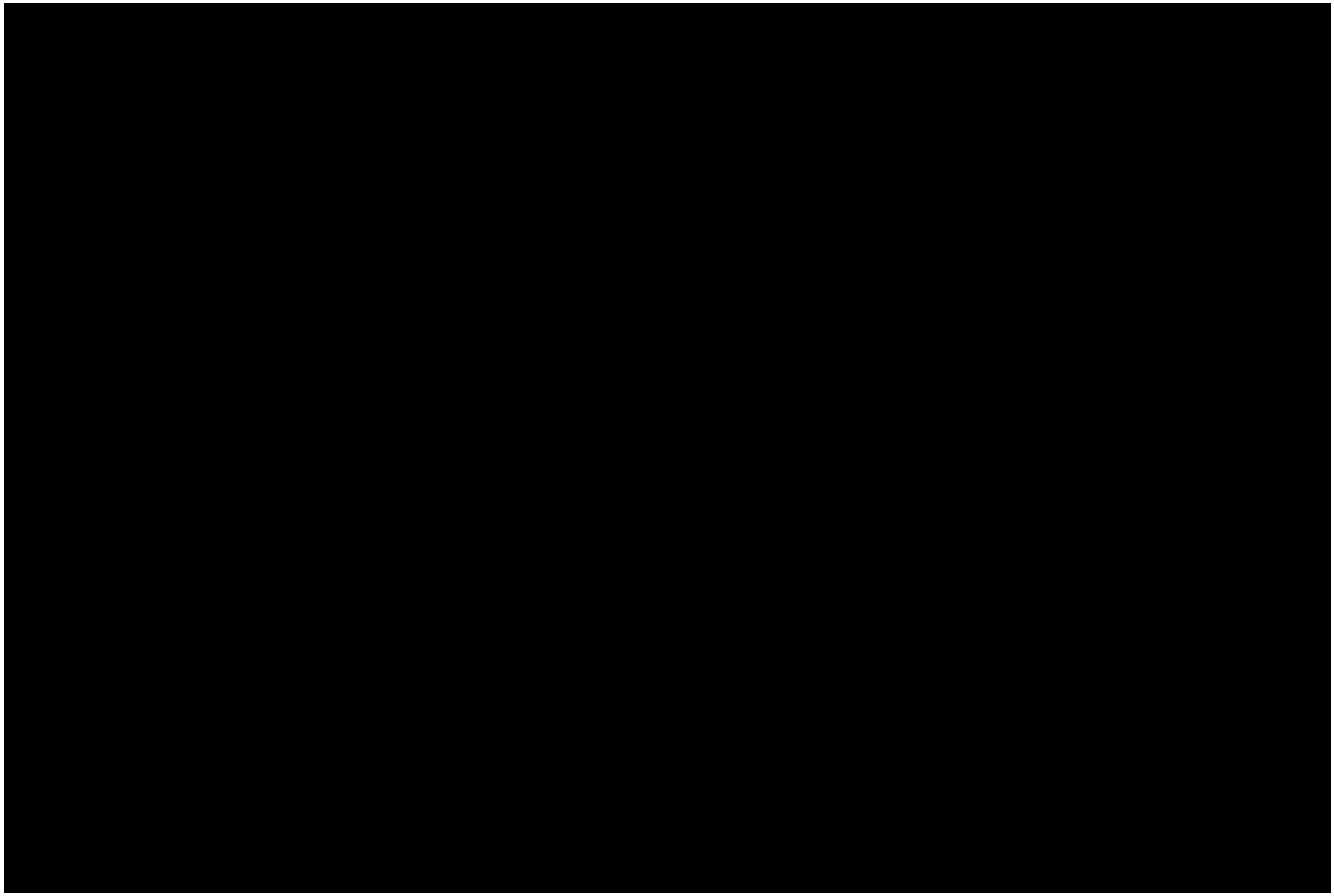
[redacted]

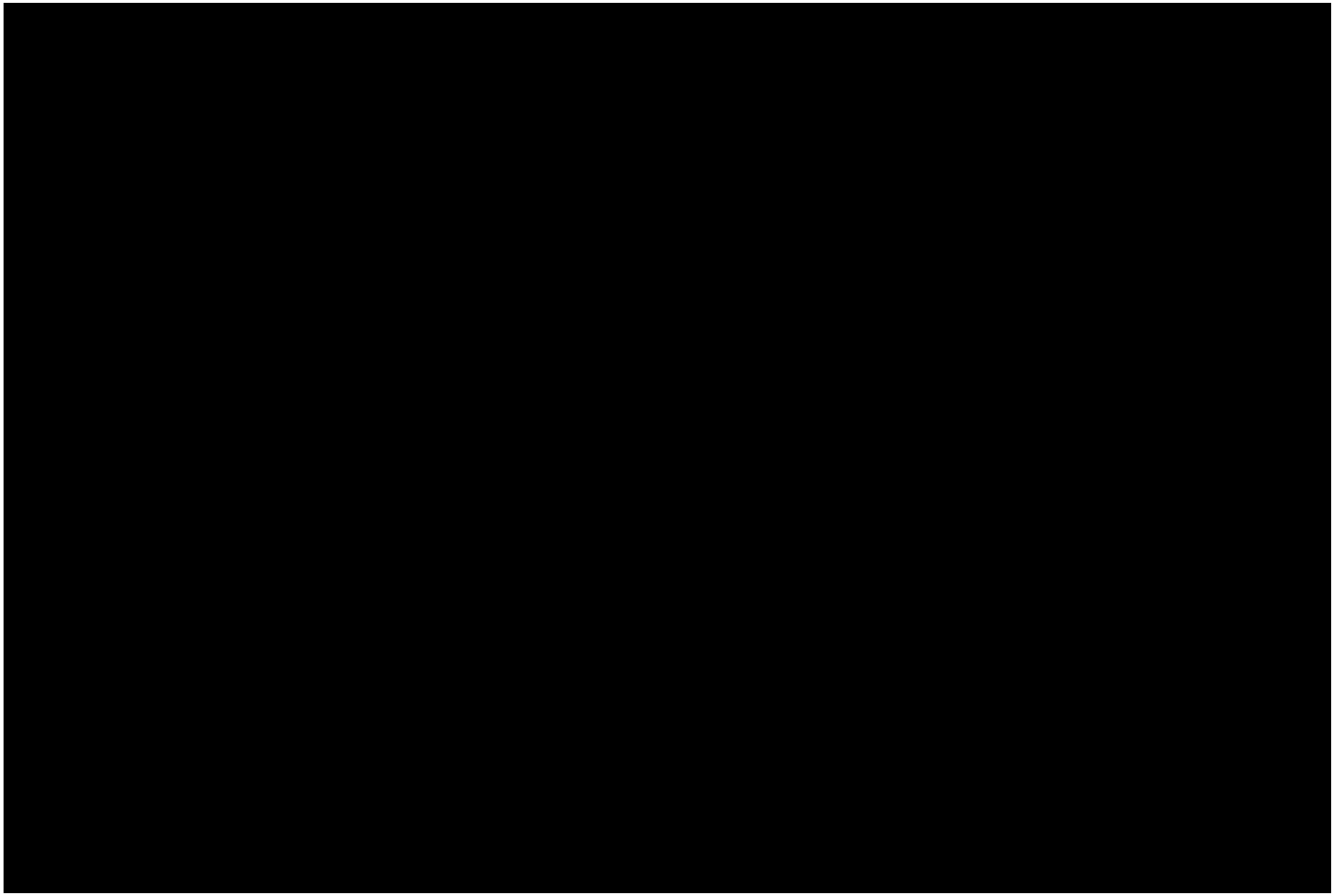












Appendix 10
Quality of Life in Inflammatory Bowel Disease Questionnaire (IBDQ)

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

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.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from

1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

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

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

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

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 SATISFIED MOST OF THE TIME, HAPPY
6 VERY SATISFIED MOST OF THE TIME, HAPPY
7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

Appendix 11
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	❑

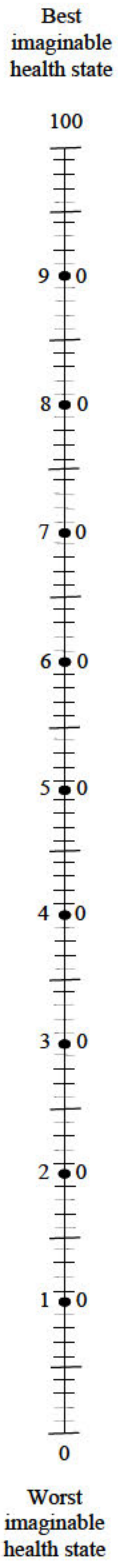
Anxiety/Depression

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



Appendix 12
Nancy Histological Index

Histologic activity on colon biopsies will be measured using the Nancy histological index (below). Histologic remission is defined as a Nancy histological index of 0–1 based on consensus guidelines recommending that histologic remission should be defined by the absence of neutrophils in the crypts and lamina propria.

Nancy Histological Index (NHI)

Marker	*Assessment*	*NHI Grade*
Erosion or ulceration	*Present*	*4: Severely active disease*
Acute inflammatory infiltrate	*Moderate to severe*	*3: Moderately active disease*
	Mild	*2: Mildly active disease*
Chronic inflammatory infiltrate	*Moderate or marked increase*	*1: Chronic inflammatory infiltrate with no acute inflammatory infiltrate*
	No or mild increase	*0: No histologically significant disease*

Histologic remission: NHI ≤1

References

Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, et al. Development and validation of the Nancy histological index for UC. Gut 2017;66:43–9.

Marchal-Bressenot A, Scherl A, Salleron J, et al. A practical guide to assess the Nancy histological index for UC. Gut 2016;65:1919–20.