Official Title: A Phase I, Open-Label, Randomized, Pharmacokinetic, Pharmacodynamic, and Safety Study of Etrolizumab Followed by Open-Label Extension and Safety Monitoring in Pediatric Patients From 4 Years to Less Than 18 Years of age With Moderate to Severe Ulcerative Colitis or Moderate to Severe Crohn's Disease

NCT Number: NCT03478956

Document Dates: Protocol Version 4: 28-May-2021

PROTOCOL

TITLE:	**A PHASE I, OPEN-LABEL, RANDOMIZED, PHARMACOKINETIC, PHARMACODYNAMIC, AND SAFETY STUDY OF ETROLIZUMAB FOLLOWED BY OPEN-LABEL EXTENSION AND SAFETY MONITORING IN PEDIATRIC PATIENTS FROM 4 YEARS TO LESS THAN 18 YEARS OF AGE WITH MODERATE TO SEVERE ULCERATIVE COLITIS OR MODERATE TO SEVERE CROHN'S DISEASE**
PROTOCOL NUMBER:	CA40192
VERSION NUMBER:	4
EUDRACT NUMBER:	2017-003649-10
IND NUMBER:	100366, 119725
TEST PRODUCT:	Etrolizumab (PRO145223, RO5490261)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
28-May-2021 16:41:31	[redacted]	[redacted]

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocol		
Version	**Date Final**	**Country**	**Version**	**Date Final**
4	See electronic date stamp on title page	—	—	—
3	22 November 2019	—	—	—
2	9 August 2018	—	—	—
1	15 October 2017	Germany	2	27 March 2018

PROTOCOL AMENDMENT, VERSION 4:
RATIONALE

Protocol CA40192 has been amended to clarify the 12-week safety follow up period after completion or early termination of the open-label extension phase, to add results from completed Phase III ulcerative colitis studies, and to add coronavirus disease 2019 (COVID-19) vaccine-related language. Changes to the protocol, along with a rationale for each change, are summarized below:

- Sections 1.3, 1.4, 1.5, 5.1.1, and Table 4 have been updated to include safety and efficacy results from completed Phase III studies in ulcerative colitis.
- Section 3.1, Appendix 1e, Figure 2, and Figure 3 have been updated and Appendix 1d has been added to clarify the 12-week long safety follow-up period after completion or early termination of the open-label extension phase.
- Guselkumab has been removed from the list of prohibited therapy (Section 4.4.3).
- The Medical Monitor has been updated in Section 5.4.1.
- COVID-19 vaccine-related language has been added to Section 4.4.1.1.
- Language has been added to indicate that the Informed Consent Form will instruct female patients to inform the investigator if they become pregnant (Section 5.4.3.1).
- Language regarding investigator reporting of pregnancies has been clarified (Section 5.4.3.2).
- The name of a Roche policy on data sharing has been corrected (Section 9.5).
- Appendix 1c has been updated to include visits during the open-label extension phase for conducting pregnancy tests.

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE I, OPEN-LABEL, RANDOMIZED, PHARMACOKINETIC, PHARMACODYNAMIC, AND SAFETY STUDY OF ETROLIZUMAB FOLLOWED BY OPEN-LABEL EXTENSION AND SAFETY MONITORING IN PEDIATRIC PATIENTS FROM 4 YEARS TO LESS THAN 18 YEARS OF AGE WITH MODERATE TO SEVERE ULCERATIVE COLITIS OR MODERATE TO SEVERE CROHN'S DISEASE**
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VERSION NUMBER:	4
EUDRACT NUMBER:	2017-003649-10
IND NUMBER:	100366, 119725
TEST PRODUCT:	Etrolizumab (PRO145223, RO5490261)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE I, OPEN-LABEL, RANDOMIZED, PHARMACOKINETIC, PHARMACODYNAMIC, AND SAFETY STUDY OF ETROLIZUMAB FOLLOWED BY OPEN-LABEL EXTENSION AND SAFETY MONITORING IN PEDIATRIC PATIENTS FROM 4 YEARS TO LESS THAN 18 YEARS OF AGE WITH MODERATE TO SEVERE ULCERATIVE COLITIS OR MODERATE TO SEVERE CROHN'S DISEASE**
PROTOCOL NUMBER:	CA40192
VERSION NUMBER:	4
EUDRACT NUMBER:	2017-003649-10
IND NUMBER:	100366, 119725
TEST PRODUCT:	Etrolizumab (PRO145223, RO5490261)
PHASE:	I
INDICATIONS:	Moderate to severe ulcerative colitis; moderate to severe Crohn's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate pharmacokinetics, pharmacodynamics and safety of etrolizumab in pediatric patients of 4 to <18 years of age with moderate to severe ulcerative colitis (UC) or with moderate to severe Crohn's disease (CD).

This study will consist of multiple phases; a randomized treatment phase that will evaluate pharmacokinetics, pharmacodynamics, and safety, followed by an open-label extension (OLE) phase, and then a progressive multifocal leukoencephalopathy (PML) monitoring phase. The objective of the 24-week randomized treatment phase is to evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of etrolizumab in pediatric patients from 4 to <18 years of age with moderate to severe UC or moderate to severe CD. The objective of the 312-week (6-year) OLE phase is to assess the long-term safety and efficacy of etrolizumab in pediatric patients from the randomized treatment phase. The objective of the 104–week PML safety-monitoring phase *(that includes the 12-week safety follow-up period after completion or early discontinuation from the OLE)* is to assess safety with focus on the occurrence of PML in patients who are no longer on etrolizumab.

Objectives and Corresponding Endpoints for the Randomized Treatment Phase

Primary Objective	Corresponding Endpoints
• To evaluate the pharmacokinetics and pharmacodynamics of etrolizumab in a pediatric IBD patient population	• PK parameters: C_{max}, AUC_{tau}, $t_{1/2}$, C_{trough} • PD parameters: β7 receptor occupancy by flow cytometry on peripheral blood lymphocytes
Safety Objective	**Corresponding Endpoints**
• To evaluate the overall safety and tolerability of etrolizumab in pediatric population	• Incidence and severity of infection-related adverse events • Incidence of immunogenic responses (ADAs) • Incidence and severity of hypersensitivity reaction events
Exploratory Objectives	**Corresponding Endpoints**
• To evaluate additional pharmacodynamic biomarkers of etrolizumab • To evaluate clinical disease biomarkers with etrolizumab treatment • To evaluate the clinical efficacy of etrolizumab	• Changes in serum MAdCAM-1 • Changes in serum CRP and fecal calprotectin • Clinical response at Week 16, as assessed by the PUCAI (UC) and PCDAI (CD)

ADA = anti-drug antibody; AUC_{tau} = area under the concentration–time curve within a dosing interval; CD=Crohn's disease; C_{max} = maximum concentration observed; CRP = C-reactive protein; C_{trough} = steady-state concentration at the end of a dosing interval; IBD=inflammatory bowel disease; MAdCAM-1 = mucosal vascular addressin cell adhesion molecule-1; PD = pharmacodynamic; PK = pharmacokinetic; PCDAI = Pediatric Crohn's Disease Activity Index; PUCAI = Pediatric Ulcerative Colitis Activity Index; $t_{1/2}$ = elimination half-life; UC=ulcerative colitis.

Objectives and Corresponding Endpoints for the Open-label Extension Phase

Safety Objective	Corresponding Endpoints
• To evaluate long-term safety of etrolizumab in pediatric population	• Incidence and severity of infection-related adverse events • Incidence and severity of malignancies • Incidence of ADAs to etrolizumab • Incidence and severity of hypersensitivity reactions
Efficacy Objective	**Corresponding Endpoint**
• To evaluate long term efficacy of etrolizumab in pediatric population	• Clinical response at Week 132, as assessed by the PUCAI (UC) and PCDAI (CD)

ADA = anti-drug antibody; CD=Crohn's disease; PCDAI = Pediatric Crohn's Disease Activity Index; PUCAI = Pediatric Ulcerative Colitis Activity Index; UC=ulcerative colitis.

Objectives and Corresponding Endpoints for the Progressive Multifocal Leukoencephalopathy Monitoring Phase

Safety Objective	Corresponding Endpoint
• Post-trial safety surveillance with focus on PML monitoring in patients who have stopped treatment	• Occurrence of confirmed PML events

PML = progressive multifocal leukoencephalopathy.

Study Design

Description of Study

This pediatric pharmacokinetic (PK)/pharmacodynamic (PD) study consists of multiple phases. The randomized treatment phase is an open-label, randomized phase in which etrolizumab is administered to patients on the basis of body weight (mg/kg); randomization will be stratified by weight (< 40 kg, ≥ 40 kg). Patients will be randomized in a 1:1 ratio to receive either high-frequency etrolizumab once every 4 weeks (Q4W) or low-frequency etrolizumab once every 8 weeks (Q8W). The high-frequency dose of 1.5 mg/kg etrolizumab will be administered Q4W (Weeks 0, 4, 8, and 12). The low-frequency dose of 3.0 mg/kg etrolizumab will be administered Q8W (Weeks 0 and 8).

After the 24–week randomized treatment phase (which includes a 16–week treatment period and an 8–week safety follow-up period), patients will then have the option to participate in the 312–week OLE phase (treatment with etrolizumab 1.5 mg/kg will be administered Q4W). All patients who participate in the 24–week randomized treatment phase and the 312–week OLE phase *will enter the 12–week safety follow up period (no etrolizumab treatment) and will* complete *the* safety surveillance PML monitoring phase (no etrolizumab treatment *for a total of 104 weeks*). All patients who choose not to enter the OLE after the 24–week randomized treatment phase will be offered participation in the 104-week PML monitoring phase.

Patients can enter the OLE phase after completion of the 24–week randomized treatment phase. If the last visit of the randomized treatment phase and Day 1 of the OLE occur on the same day, the assessments from the randomized treatment phase should be completed. The assessments from the randomized treatment phase can apply to the OLE assessments (i.e., the same assessments should not be repeated for the OLE).

The 104–week PML monitoring phase will consist of telephone calls approximately every 6 months with administration of the PML Subjective Checklist. If there are any signs or symptoms suggestive of PML identified on this subjective checklist during the telephone call, the patient will be asked to come into the clinic for a neurologic examination. The PML Algorithm will be followed for any suspected case of PML, and any confirmed case of PML will be reported as a serious adverse event.

Patients who experience clinically significant worsening in their UC or CD status during the study can receive rescue therapy based on current standard of care. Patients can receive rescue therapy at any time during the study, including the treatment phase, safety follow–up phase, OLE phase and PML monitoring phase.

Approximately 24 pediatric patients from 4 to <18 years of age with moderate to severe UC or with moderate to severe CD will be enrolled to target at least 12 patients with evaluable PK profiles. At least 4 patients from 4 years to <12 years of age should be enrolled. This study requirement is according to the health authority requirement. If PK and PD samples are missing, patients will be replaced at the discretion of the sponsor. Every effort should be made to collect all PK and PD samples.

Patients who initially failed screening may be rescreened twice at the discretion of the investigator.

If a patient fails any laboratory inclusion/exclusion criteria at screening the investigator may repeat the test twice within the screening period. If the patient fails the laboratory criteria for a third time they will be considered a screen failure. It will not be considered a re-screening if blood samples have to be redrawn due to sample handling problems, breakage, or sample integrity. This multi-center study will be conducted at global sites.

Rescue therapy can be prescribed based on the discretion of the investigator and disease flare, and can include methotrexate, corticosteroids, immunomodulators, and excludes anti-TNFs, vedolizumab and other biologic agents. Based on the patient's disease status and physicians care practices, the patient can be withdrawn from the study at any time to receive excluded therapy.

Number of Patients

A minimum of 12 patients with UC and CD from 4 years to <18 years of age will be enrolled in the study. There will be at least 4 children from 4 years to <12 years of age with evaluable PK profiles, which is a study obligation according to the health authority requirement.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form by parent or legal guardian
- Age of 4 years to <18 years at the time of signing the Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Weight of 13 kg or more
- Diagnosis of UC or CD confirmed by biopsy and established for ≥3 months (i.e., after first diagnosis by a physician according to American College of Gastroenterology [ACG] guidelines) prior to screening
- Inadequate response, loss of response or intolerance to prior immunosuppressants and/or corticosteroid treatment and/or anti-TNF therapy
- For patients with UC: moderately to severely active UC as determined by an MCS of 6–12 with an endoscopic subscore ≥2 (within the last 12 months prior to screening) and a rectal bleeding subscore ≥1
- For patients with CD: moderately to severely active CD as determined by a Pediatric Crohn's Disease Activity Index (PCDAI) score of >30 at baseline
- Patients must meet the following surveillance colonoscopy requirements:
  - Document evidence of surveillance for dysplasia every 1 to 2 years, beginning approximately 7 to 10 years after their initial diagnosis
- For postpubertal females of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods during the treatment period and for at least 24 weeks after the last dose of etrolizumab.

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

  Examples of acceptable contraceptive methods include bilateral tubal ligation, male sterilization, combined oral contraceptive pill or transdermal patch, spermicide and barrier [condoms], intrauterine device, implants for contraception, injections for contraception [with prolonged release], hormonal vaginal device.

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

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

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

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
- 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
- Abdominal abscess
- A history or current evidence of colonic mucosal dysplasia
- Patients with fixed symptomatic stenosis of the intestine
- Patients with history or evidence of adenomatous colonic polyps that have not been removed
- Patients who are not up to date on vaccinations per the local vaccine schedule will be excluded.

Exclusion Criteria Related to Ulcerative Colitis

- Severe extensive colitis per investigator judgment that colectomy is imminent OR the patient has two of the following five symptoms at screening or baseline visit:
  - 6 bowel movements daily with obvious blood
  - Abdominal examination worrisome for imminent surgery
  - Persistent fever
  - Tachycardia
  - Anemia (hemoglobin $<$ 8 g/dL)

Exclusion Criteria Related to Crohn's Disease

- Sinus tract with evidence for infection (e.g., purulent discharge) in the clinical judgment of the investigator
- Short-bowel syndrome
- Evidence of abdominal or perianal abscess
- Expected to require surgery to manage CD-related complications during the study

Exclusion Criteria Related to Prior or Concomitant Therapy

- Any prior treatment with anti-integrin agents (including natalizumab, vedolizumab, and efalizumab)
- Any prior treatment with ustekinumab
- Any prior treatment with anti-adhesion molecules (e.g., anti-MAdCAM-1)
- Any prior treatment with rituximab
- Use of IV steroids within 30 days prior to screening with the exception of a single administration of IV steroid
- Use of agents that deplete B or T cells (e.g., alemtuzumab or visilizumab) within 12 months prior to Day 1, with the exception of AZA and 6-MP
- Use of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) within 4 weeks prior to Day 1
- Use of other biologics (e.g., anti-TNF) within 8 weeks before dosing, unless drug level is below detectability before completion of the 8-week interval
- 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.)
- Apheresis (i.e., Adacolumn® apheresis) within 2 weeks prior to Day 1

- Received any investigational treatment including investigational vaccines within 12 weeks prior to Day 1 of the study or 5 half-lives of the investigational product, whichever is greater
- 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)

Exclusion Criteria Related to General Safety

- Pregnant or lactating
- Lack of peripheral venous access
- Congenital or acquired immune deficiency
- Hospitalized (other than for elective reasons) during the screening period
- Inability to comply with study protocol, in the opinion of the investigator
- Significant uncontrolled comorbidity, such as cardiac (e.g., moderate to severe heart failure New York Heart Association [NYHA] Class III/IV), pulmonary, renal, hepatic, endocrine, or GI disorders (excluding UC and CD)
- Neurological conditions or diseases that may interfere with monitoring for PML
- History of demyelinating disease
- Clinically significant abnormalities on the screening PML Subjective Checklist
- History of major neurological disorders, including stroke, multiple sclerosis, brain tumor, neurodegenerative disease, or poorly controlled epilepsy
- History of alcohol, drug, or chemical abuse $<$6 months prior to screening
- Conditions other than UC or CD that could require treatment with $>$10 mg/day of prednisone (or equivalent) during the course of the study
- Presence of metal in the body that could pose a hazard during any potential scanning in patients for whom a magnetic resonance imaging (MRI) scan is considered unsafe
- History of cancer, including hematologic malignancy, solid tumors, and carcinoma in situ, within 5 years before screening with the following caveats:
  - Local basal or squamous cell carcinoma of the skin that has been excised and is considered cured is not exclusionary.
  - A history of chronic myelogenous leukemia, hairy cell leukemia, melanoma, renal cell carcinoma, or Kaposi sarcoma is exclusionary, irrespective of the duration of time before screening.
  - History of a cervical smear indicating the presence of adenocarcinoma in situ (AIS), high-grade squamous intraepithelial lesions (HSIL), or cervical intraepithelial neoplasia (CIN) of Grade $>$1 is exclusionary, irrespective of the duration of time before screening.

Exclusion Criteria Related to Infection Risk

- Congenital or acquired immune deficiency
- Patients must undergo screening for HIV and test positive for preliminary and confirmatory tests
- Positive hepatitis C virus (HCV) antibody test result, unless the patient (1) has undetectable HCV RNA levels for $>$6 months after completing a successful course of HCV anti-viral treatment and an undetectable HCV RNA at screening or (2) has a known history of HCV antibody positivity with a history of undetectable HCV RNA 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 is positive, the patient is not eligible for this study.
  - In the event the HBV DNA test cannot be performed, the patient is not eligible for this study.
  - If the HBV DNA test is negative, the patient is eligible for this study. These patients will undergo periodic monitoring for HBV DNA during the study.
- Positive stool test result for ova or parasites or positive stool culture for pathogens at time of screening
- Evidence of or treatment for *Clostridium difficile* (as assessed by *C. difficile* toxin testing) within 60 days prior to Day 1or 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 sample is required during screening evaluation only if clinical suspicion is high and to determine the need for CMV treatment
- History of active or latent treated TB, regardless of treatment history)
  - Patients with a history of active or latent TB (based on a positive screening assay, either purified protein derivative [PPD] skin test or QuantiFERON®-TB Gold test, 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.
- Suspicion of active TB on chest radiograph (X-ray, posteroanterior and lateral) taken within 3 months of randomization
- History of recurrent opportunistic infections and/or history of severe disseminated viral infections (e.g., herpes)
- Opportunistic infection within 3 months before screening
- 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/CD 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 Values (at Screening)

- Serum creatinine >1.5 times upper limit of normal (ULN)
- ALT or AST >3 ULN, or alkaline phosphatase >3 ULN, or total bilirubin >2.5 ULN (unconjugated hyperbilirubinemia that is associated with known Gilbert's syndrome is not an exclusion criterion)

- In patients with diabetes*:* glycosylated hemoglobin (HbA_{1c}) > 8.0%
- Platelet count <100,000/mL
- Hemoglobin <8 g/dL
- Absolute neutrophil count <1500/mL
- Absolute lymphocyte count <500/mL

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for PK/PD or statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur 108 months after the last patient is enrolled.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 9 years.

The randomized treatment phase will continue for 24 weeks (includes a 16–week treatment period and an 8–week safety follow-up period) after the last patient is enrolled into the study or until the sponsor decides to terminate the study, whichever is earlier. Patients who withdraw from the treatment period should complete the 8–week safety follow-up period. All patients will be offered participation in the 104–week extended PML monitoring phase.

The OLE phase will continue for approximately 6 years after the last patient is enrolled into the study or until the Sponsor decides to terminate the study, whichever is earlier.

The PML monitoring phase will last 104 weeks for patients who enter, either from the randomized treatment phase or the OLE phase *(includes 12-week safety follow-up period after completion or early discontinuation from OLE).*

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal product (IMP) for this study is etrolizumab. All patients will receive etrolizumab one subcutaneous injection of 0.01 mL per kg of patient weight (1.5 mg/kg) Q4W or injection of 0.02 mL per kg of patient weight (3 mg/kg) Q8W.

Statistical Methods

Primary Analysis

The primary analysis of the study will be performed when all the data from the randomized controlled part of the study are in the database and has been cleaned and verified.

Determination of Sample Size

A sample size of 12–16 patients has been considered sufficient in order to evaluate the PK and PD endpoints. No formal sample size and power calculations were performed.

Pharmacokinetic Analyses

The PK analysis population will consist of patients with sufficient data to enable estimation of key parameters such as AUC (area under the curve), C_{max} (maximum concentration), C_{trough} (trough concentration) and $t_{1/2}$ (elimination half-life).

Non-compartmental analysis will be used to derive PK parameters including C_{max} and T_{max} after the first and final dose, $t_{1/2}$, AUC within dosing interval (AUC_{84-112}) and (AUC_{56-112}) for 1.5 mg/kg Q4W and 3 mg/kg Q8W, respectively.

All PK parameters will be listed and summarized by descriptive summary statistics including means, geometric means, ranges, standard deviations, and coefficients of variation.

Individual and mean concentration versus time data will be tabulated and plotted by dose level.

PK data from this study may be combined with data from the adult study to perform a population PK analysis. Population typical value of PK parameters will be estimated for the entire study population, along with estimates of intra- and inter-patient variance and an estimate of random error. Individual patient parameter estimates will be computed using the post hoc analysis

procedure. A prospective analysis plan will be prepared, and the population PK analysis will be presented in a report separate from the Clinical Study Report of this study.

Additional exploratory PK/PD analyses or modeling may be conducted as appropriate.

Pharmacodynamic Analyses

All PD parameters will be listed and summarized by descriptive summary statistics including means, standard deviations, medians, ranges, and coefficients of variation.

Safety Analyses

The safety analysis population will consist of all patients who received at least one dose of study drug, with patients grouped according to dose regimen received.

Safety will be assessed through descriptive summaries of adverse events (including serious adverse events, malignancies, infections – in particular gastrointestinal infections, systemic hypersensitivity events, and injection site reactions), laboratory test results, and vital signs.

Immunogenicity Analyses

The immunogenicity analysis population will consist of all patients with at least one anti-drug antibody (ADA) assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after etrolizumab treatment (post-treatment incidence) will be summarized by treatment group. When determining post treatment incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but developed an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and PD endpoints will be assessed and reported via descriptive statistics.

Biomarker Analyses

Beta 7 receptor occupancy and serum MAdCAM-1 results will be summarized by dosing group and timepoints as absolute values and/or change from baseline. Summary statistics may be provided.

A PK/PD model may be developed to evaluate the PK/PD relationship after combining data from adult's study. This modeling work will be reported separately outside the Clinical Study Report of this study.

Exploratory Analyses

PUCAI/PCDAI response or remission rates will be summarized descriptively over time within each treatment group. Disease activity scores and subscores, fecal calprotectin levels and serum C-reactive protein (CRP) levels and their change from baseline will also be summarized descriptively over time to assess the efficacy of etrolizumab in reducing signs and symptoms of disease and levels of inflammatory biomarkers.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
ACG	American College of Gastroenterology
ADA	anti-drug antibody
AIS	adenocarcinoma in situ
AUC	area under the concentration-time curve
AUC_{τ}	area under the concentration-time curve within the last dose interval
AUC_{inf}	area under the concentration-time curve from time zero to infinity
AZA	azathioprine
BCG	Bacille Calmette-Guerin
CD	Crohn's disease
CIN	cervical intraepithelial neoplasia
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	*coronavirus disease 2019*
COA	clinical outcome assessment
CRP	C-reactive protein
C_{max}	maximum serum concentration observed
C_{trough}	steady-state concentration at the end of a dosing interval (i.e., just prior to next drug administration)
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
EU	European Union
FDA	(U.S.) Food and Drug Administration
HBV	hepatitis B virus
anti-HBc total	HBV core antibody total
HBcAb	HBv core anti-body
HBsAg	HBV surface antigen
HCP	health care provider
HCV	hepatitis C virus

Abbreviation	Definition
HIPAA	Health Insurance Portability and Accountability Act
HSIL	High-grade squamous intraepithelial lesion
ICH	International Council for Harmonisation
IBD	inflammatory bowel disease
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
JCV	John Cunningham virus
LD	loading dose
LPLV	last patient, last visit
MAbs	monoclonal antibodies
MAdCAM	mucosal vascular addressin cell adhesion molecule
MCS	Mayo Clinic Score
MMF	mycophenolate mofetil
MRI	magnetic resonance imaging
MTX	methotrexate
NCI	National Cancer Institute
NGS	next-generation sequencing
NOAEL	no-observed-adverse-effect-level
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OLE	open-label extension
PCDAI	Pediatric Crohn's Disease Activity Index
PCR	polymerase chain reaction
PD	pharmacodynamics
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PopPK	population PK
PPD	purified protein derivative
PUCAI	Pediatric Ulcerative Colitis Activity Index
Q4W	every 4 weeks
Q8W	every 8 weeks
QOL	quality of life
RBR	Research Biosample Repository
RO	receptor occupancy
SC	subcutaneous
SPC	Summary of Product Characteristics

Abbreviation	Definition
$t_{1/2}$	elimination half-life
TB	tuberculosis
t_{max}	time to maximum observed concentration
TNF-α	tumor necrosis factor–alpha
UC	ulcerative colitis
U.S.	United States
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON PEDIATRIC 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 disease can affect any age group, but occurrence peaks between the ages of 15 and 35 years.

Pediatric-onset UC affects both sexes equally, with the mean age of diagnosis of approximately 12 years of age (Kugathasan et al. 2003). The annual incidence of UC reported among United States (U.S.) pediatric populations <18 years of age is 0.45–4.9 per 100,000 (Abramson et al. 2010; Benchimol et al. 2011). Benchimol et al. summarized all pediatric IBD studies published to date, globally, and found incidence ranged generally 0–6 per 100,000, with a few exceptions (Benchimol et al. 2011).

More recent nationwide European studies conducted among pediatric populations <18 years of age indicate that incidence differs by country; higher rates were reported in Finland and Denmark (4–9 and 6.2–7.2 per 100,000, respectively) while comparatively lower rates were reported in Slovenia, Iceland, Scotland, and Spain (2.9, 2.4, 2.06, and 0.88 per 100,000, respectively; Lehtinen et al. 2011; Henderson et al. 2012; Agnarsson et al. 2013; Martín-de-Carpi et al. 2013; Urlep et al. 2015; Larsen et al. 2016). It is rarely seen in patients <4 years of age; the annual incidence in this age group is 0.2–0.7 per 100,000 and the prevalence is 1.1–2.3 per 100,000 (Herrinton et al. 2008; Abramson et al. 2010; Malaty et al. 2010). Combining the range of age-specific UC prevalence estimates reported in the literature with the age-specific 2013 U.S. population estimates, the number of children <18 years of age diagnosed with UC is estimated to be between 10,400 and 14,600 in the U.S.

The goals of treatment, both in adult and pediatric patients, are to induce and maintain remission, decrease corticosteroid use (as measured by steroid-free remission), induce mucosal healing, reduce hospitalization and surgery, improve health-related quality of life (QOL), and avoid disability. For mildly to moderately active UC, oral and rectal preparations of 5-aminosalicylate (5-ASA) medications are used either alone or together and result in remission in approximately 50% of patients. Patients whose UC fails to

respond to 5-ASA drugs or who have moderately to severely active UC often receive conventional therapy, including corticosteroids and immunomodulator therapy (e.g., azathioprine [AZA], 6-mercaptopurine [6-MP], and methotrexate [MTX]). Corticosteroids achieve remission in about 70% of patients, but approximately 20% become steroid dependent and only half maintain steroid-free remission (Faubion et al. 2001).

The systemic toxicities of chronic corticosteroid use include adrenal suppression, infection, growth failure, insulin resistance, cataracts, osteoporosis, and glaucoma. Mood disturbances and sleep disorders are also common with steroid treatment (Turner et al. 2012). These side effects, in particular growth failure, bone loss, and glucose intolerance with corticosteroids, are particularly detrimental to pediatric patients with UC because they occur at a critical growth and development period. Immunomodulators, such as 6-MP, AZA, and MTX, have also been used to achieve steroid-free remission, but efficacy in maintaining steroid-free remission is modest (Lobel et al. 2004; Chebli et al. 2010; Mañosa et al. 2011; Khan et al. 2013). In addition, these medications are associated with significant side effects, including hepatotoxicity, pancreatitis, and bone marrow suppression.

More recently, monoclonal antibodies (MAbs) targeting tumor necrosis factor–alpha (TNF-α), such as infliximab (Remicade®) and adalimumab (Humira®), have been used to induce and maintain remission in patients whose immunomodulatory therapy fails, are steroid dependent or refractory, and have moderately to severely active UC. These biologic agents induce remission in up to 40% of patients, but sustained remission is seen in only 10%–20% of patients over 1 year (Rutgeerts et al. 2005; Sandborn et al. 2013). Importantly, anti-TNF therapies are associated with serious adverse events, such as bacterial infection, including tuberculosis (TB), disseminated fungal infections, lymphoma, and demyelination (Chang and Lichtenstein 2006). Infliximab was approved for use in pediatric patients aged 6–17 years in Europe and in the United States (U.S.) in 2011 following a Phase III safety and efficacy trial, which demonstrated approximately 30% 1-year remission rates (Hyams et al. 2012). *Adalimumab has also been approved for use in pediatric patients age 6 years of age and older with UC and Crohn's disease (CD) in the U.S. (Humira, U.S Package Insert).*

Additionally, in the pivotal studies for vedolizumab, an anti-integrin approved for the treatment of UC in adults, 47% of patients with UC had a clinical response with 6 weeks of induction treatment. Up to 45% of patients with UC who were vedolizumab responders at the end of induction achieved remission with 46 weeks of maintenance treatment, compared with 16% of UC patients, given placebo (Sandborn et al. 2013; Feagan et al. 2013). Though vedolizumab is not approved for pediatric use, it has been used off label in both CD and UC. A retrospective review of pediatric patients with CD and UC <18 years of age shows that patients receiving vedolizumab appear to respond to treatment (Singh et al. 2016).

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

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

1.2 BACKGROUND ON PEDIATRIC CROHN'S DISEASE

CD is a chronic, relapsing form of IBD that can affect any portion of the gastrointestinal (GI) tract, with 40%–50% of cases affecting the small bowel. CD is characterized by patchy, transmural inflammation, ulcers, and granulomatous lesions that are interspersed with healthy sections of bowel (skip lesions). The disease is progressive; uncontrolled inflammation develops into stricturing or penetrating complications such as prestenotic dilatation, obstruction (stricturing), and intra-abdominal or perianal fistulas and abscesses (penetrating). Clinical signs and symptoms include chronic diarrhea, abdominal pain, cachexia, abdominal mass, or tenderness as well as the overt signs of fistulas.

Pediatric-onset CD affects both sexes with an increased prevalence in males (Abramson et al. 2010). Approximately 20% of affected adults develop CD before 20 years of age (Kappelman et al. 2013). In a Belgium cohort, the median age at presentation of pediatric CD is approximately 12.5 years and presentation rarely occurred before 4 years of age (de Greef et al. 2013).

An overall trend of increasing rates of pediatric IBD, primarily due to the rising incidence of CD, has been reported throughout the world (Benchimol et al. 2011). The incidence of CD in pediatric patients from Wisconsin was estimated to be approximately 4.6/100,000 persons per year in one study (Kugathasan et al. 2003), and in a separate study, the prevalence of CD in patients <20 years of age was 43 per 100,000 using U.S. health insurance claims data (Kappelman et al. 2007).

So far, there is no cure for CD. The selection of appropriate medical therapy depends upon an understanding of the location of the disease, its severity, and the complications the patient experiences. The treatment goals for CD are to induce and maintain

remission, induce mucosal healing, avoid surgery, and improve quality of life (Lichtenstein et al. 2009; Van Assche et al. 2010).

Systemic corticosteroids have been the mainstay treatment for inducing remission and are effective in approximately 80% of patients (Summers et al. 1979; Malchow et al. 1984). However, they are less effective as a maintenance therapy, with only 28% of patients achieving a prolonged response after 1 year of treatment and 32% of patients becoming steroid dependent (Faubion et al. 2001; Peyrin-Biroulet et al. 2010). Corticosteroid-induced toxicities and side effects as described previously are detrimental in the pediatric population because of their critical period of growth and development; 50% of patients will stop their treatment because of these side effects.

Immunosuppressants (e.g., AZA, 6-MP, or MTX) are typically administered to induce remission in patients who are intolerant of or refractory to steroids and to maintain remission in patients who achieve quiescent CD. Immunosuppressants are given with or without a steroid bridge, depending on a patient's symptoms during the 2- to 4-month onset of immunosuppressant efficacy.

The development of MAbs against TNF-α has provided an additional treatment option. Although anti-TNFs are effective in a significant proportion of patients, efficacy is suboptimal; remission rates after 4 weeks of induction therapy are lower than 35% and, among patients who respond to induction therapy, fewer than 50% have achieved remission when assessed in maintenance at 20–30 weeks (Peyrin-Biroulet et al. 2011). Furthermore, 30% of patients are reported to be primary non-responders to anti-TNF therapy when assessed after 4 weeks of induction therapy (Targan et al. 1997; Sandborn et al. 2007). Anti-TNFs are also associated with significant side effects, including serious infection, opportunistic infection, lupus-like reactions, and an increased risk of lymphoma (Siegal and Melmed 2009). Tolerability concerns include injection site reactions, occurring in 10% of patients receiving adalimumab (van der Heijde et al. 2006), and infusion reactions, occurring in 9%–17% of patients treated with infliximab (de Vries et al. 2011).

The anti-integrins are another class of biologics approved for the treatment of CD. Natalizumab (Tysabri®) is an anti-integrin approved in the United States for the treatment of moderate to severely active CD. The use of natalizumab, which blocks both $\alpha4\beta1$ and $\alpha4\beta7$ integrins, has been limited because of concerns that inhibition of $\alpha4\beta1$/vascular cell adhesion molecule 1 (VCAM-1) binding increases the risk of progressive multifocal leukoencephalopathy (PML), a rare but serious infection of the central nervous system (CNS).

Vedolizumab is the most recently approved gut-selective anti-integrin for CD; it targets only the $\alpha4\beta7$ integrin receptor, inhibiting T-lymphocyte binding to the adhesion molecule, mucosal vascular addressin cell adhesion molecule (MAdCAM-1), and is administered as an IV infusion. In the pivotal trials for vedolizumab, 31% of patients had

a clinical response with 6 weeks of induction treatment; up to 39% of the vedolizumab responders achieved remission with 46 weeks of maintenance treatment, compared with 22% of patients given placebo (Sandborn et al. 2013). Though vedolizumab is not approved for pediatric use, it has been used off label in both CD and UC.
A retrospective review of pediatric patients with CD and UC <18 years of age shows that patients receiving vedolizumab appear to respond to treatment (Singh et al. 2016).

Altogether, biologic use is more common in pediatric CD than in pediatric UC, with respective estimates of 24% and 15% (ages 6-12 years) and 33% and 17% (age ≥13–17 years) of the treated population (Yang et al. 2012). Although anti-TNF-agents appear to be more effective than immunosupressants in the treatment of moderate to severe CD, the benefits of early anti-TNF use must be compared against the potential risks. Indeed, anti-TNF agents expose patients to the risks of systemic immunosuppression with the potential for serious complications such as opportunistic infections (Remicade® Summary of Product Characteristics [SPC]; Humira® SPC).

Despite a number of therapeutic options, there remains a need in pediatric patients with moderate to severe CD for agents with a strong and positive benefit-risk profile. Agents targeted at the level of the specific organ that avoid systemic immunosuppression may contribute to fulfill that need.

1.3 BACKGROUND ON ETROLIZUMAB

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 cells that have been genetically engineered to synthesize the antibody. The protein is manufactured in bioreactors and purified using a series of harvest, purification, and formulation steps. The potency of etrolizumab is determined by an in vitro assay that measures the inhibition of adhesion of $\alpha4\beta7$-expressing cells to MAdCAM–fragment crystallizable region.

Etrolizumab distinguishes itself from natalizumab and vedolizumab because it specifically binds the integrin $\beta7$ subunit, found in both $\alpha4\beta7$ (Holzmann et al. 1989; Hu et al. 1992) and $\alpha E\beta7$ integrins (Cepek et al. 1993), which regulate trafficking and retention of leukocyte/lymphocyte subsets, respectively, in the intestinal mucosa.

It is important to note that etrolizumab does not bind to $\alpha4\beta1$ (target for natalizumab), which regulates trafficking to both mucosal and non-mucosal tissues, including the CNS. Etrolizumab, therefore, represents a novel gut mucosal–selective anti-trafficking agent whose selectivity may enhance efficacy in UC and CD 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, hematologic, and cardiovascular systems). No adverse events were observed in the embryo-fetal developmental toxicity studies *and there was no evidence of increased rates of infection.*

The pharmacokinetics and pharmacodynamics of etrolizumab were characterized in Phase I (ABS4262g) and Phase II (ABS4986g) studies in adult patients with moderately to severely active UC. Study ABS4262g tested both single dose and multiple doses of etrolizumab either IV or subcutaneous (SC) at dose levels of 0.3–10 mg/kg (single dose IV), 3 mg/kg (single dose SC), 0.5–3 mg/kg SC or 4 mg/kg IV (multiple doses given once every 4 weeks [Q4W]×3). Study (ABS4986g) tested two dose regimens: 100 mg (nominal dose) SC Q4W and 420 mg SC at Week 1 followed by 300 mg SC at Weeks 2, 4, and 8. The pharmacokinetic (PK) profile of etrolizumab is generally dose proportional with regard to maximum serum concentration observed (C_{max}) and area under the serum concentration-time curve from time zero to infinity (AUC_{inf}) (or AUC within the last dose interval [AUCτ]) for the dose ranges tested. The mean elimination half-life in UC patients was approximately 13–15 days following multiple doses of 100 mg and 300 mg SC administration.

In study ABS4262g, a dose-dependent increase in the duration of β7 receptor occupancy was observed following a single IV dose of 0.3, 1 and 10 mg/kg of etrolizumab. The group mean occupancy was maintained for approximately 2 weeks, 6 weeks, and 10 weeks, respectively. In study ABS4986g, maximal/near maximal β7 receptor occupancy was observed up to 71 days following multiple doses of 100 mg and 300 mg SC administration.

Exploratory PK/pharmacodynamics (PD) analysis showed a relationship between PK (serum drug levels) and PD (β7 receptor occupancy) in which approximately 1–3 μg/mL of serum etrolizumab maintained maximal/near maximal occupancy of β7 integrin on peripheral blood mucosal-homing T cell subsets.

The safety of etrolizumab *has been* assessed in Phase I, Phase II, and *five* Phase III studies *in adult patients with moderate to severe UC.*

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

- 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 IV or SC etrolizumab.
- *The safety profile of etrolizumab in completed Phase III studies in UC was consistent with that observed in previous Phase II studies. No new or clinically significant safety signal was identified from an overall review of these studies. To date, there have been six adverse drug reactions (ADRs) identified, based on a review of pooled all exposure Phase II and III UC studies. These ADRs are Appendicitis, Arthralgia, Eczema, Fatigue, Rash, and Rash Macular.*

- *To date,* no events of PML have been reported in etrolizumab-treated patients.

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

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The purpose of this study is to assess the pharmacokinetics, pharmacodynamics, and safety of etrolizumab in pediatric patients (ages 4 years to $<$18 years) with moderately to severely active UC or moderately to severely active CD. The PK and PD information obtained from this Phase I study will be used to identify an appropriate dosing regimen for a separate Phase III safety and efficacy study in a pediatric IBD population.

A significant proportion of patients with UC will not experience a durable clinical benefit with anti-TNF agent treatment options. Furthermore, adverse events associated with anti-TNFs include elevated rates of serious bacterial infection, including TB, and (more rarely) lymphoma and demyelination (Chang and Lichtenstein 2006). No currently available therapy achieves sustained remission in more than 10%–30% of patients with IBD (Hanauer et al. 2002; Sandborn et al. 2005).

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

A global, Phase II, multicenter study (Study ABS4986g; EUCALYPTUS) designed to determine the exposure-response relationship and to further characterize the safety and tolerability of etrolizumab in treatment of adult patients with moderately to severely active UC has been completed. In this study, 120 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 1(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-naïve subgroup, clinical remission at Week 10 was observed in 43.8% of patients in the 100-mg etrolizumab group versus 0% of patients in the placebo group; clinical remission was observed 25% of patients in the 300-mg + LD group.

Favorable safety 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.

Etrolizumab is currently being studied in a global Phase III program in patients with moderate to severely active CD and UC.

An analysis of the data from completed adult Phase III studies in moderately to severely active UC (GA28948, GA28949, GA28950, GA29102, and GA29103) demonstrated that etrolizumab did not appear to consistently provide benefit over placebo and also did not provide benefit over adalimumab or infliximab. This new safety information does not change the overall benefit-risk ratio for etrolizumab.

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 have been reported *with etrolizumab use in clinical studies to date.*

Preliminary expression studies of the pharmacological target for etrolizumab, the integrin $\beta 7$ receptor, on gut CD4+ and CD8+ T cells isolated from resections of patients with UC and patients with CD suggests that expression levels are similar between both diseases. The reported efficacy of vedolizumab, an anti-$\alpha 4\beta 7$ MAb, in CD demonstrates a role for $\alpha 4\beta 7$ in the pathobiology of this disease (Sandborn et al. 2013) and suggests that etrolizumab may be efficacious. In addition, because $\alpha E\beta 7+$ expression is reportedly elevated in patients with CD (Elewaut et al. 1998; Oshitani et al. 2003) with an observed increase in expression from distal to proximal bowel, the dual mechanism of action of etrolizumab may bring enhanced efficacy in CD without generalized immunosuppression compared with available anti-integrin and anti-TNF therapies.

Considering the significant clinical and non-clinical data generated to date for etrolizumab, there is a strong rationale and a positive benefit-risk assessment for studying etrolizumab, supported by:

- Studies of an anti-$\alpha 4\beta 7$ MAb, vedolizumab, approved for the treatment of patients with moderate to severe CD or moderate to severe UC
- Completed *Phase II* studies with etrolizumab in UC demonstrating clinically meaningful benefit, as well as a full characterization of the PK/PD profile in UC and, importantly, an acceptable safety profile in previous etrolizumab studies
- Data that implicate $\alpha 4\beta 7$ receptors in the pathobiology of CD with the possibility that inhibition of the $\alpha E\beta 7$/E-cadherin interaction by etrolizumab could bring enhanced efficacy
- An acceptable safety profile in the ongoing clinical development program, and a carefully designed Phase III UC and CD program with robust safety monitoring

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

Patient safety will be monitored throughout the study via an internal safety monitoring board and periodic assessments of vital signs, safety laboratory assessments, neurological exams, and continuous review of adverse events.

Despite the lack of theoretical or experimental evidence for the specific role of β7 integrins in contributing to a risk for PML, since there is a risk of PML associated with non-selective anti-integrins, extensive risk monitoring procedures will be still in place in this study as the safety database continues to grow (see Section 5.1.1.1.1).

Patients who experience a clinical relapse in their UC or CD status will have the option to receive rescue therapy during the study (see Section 4.4.2.2).

To minimize risk pertaining to injection reactions, all SC injections of etrolizumab in this study will be administered to patients in the clinic or at home or another suitable location by a trained nursing professional, with at least a 1-hour observation period after dosing. Patients will be regularly assessed by the treating physician to ensure ongoing safety.

Since this is the first study of etrolizumab in a pediatric population, the risk and benefit in the pediatric population is unknown.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate pharmacokinetics, pharmacodynamics and safety of etrolizumab in pediatric patients of 4 to <18 years of age with moderate to severe UC or with moderate to severe CD.

This study will consist of multiple phases; a randomized treatment phase, followed by an OLE phase, and then a PML-monitoring phase. The objective of the 24–week randomized treatment phase is to evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of etrolizumab in pediatric patients from 4 to <18 years of age with moderately to severe UC or moderate to severe CD. The objective of the 312–week (6-year) OLE phase is to assess the long-term safety and efficacy of etrolizumab in pediatric patients from the randomized treatment phase. The objective of the 104–week PML safety-monitoring phase *(that includes the 12-week safety follow-up period after completion or early discontinuation from the OLE)* is to assess safety with focus on the occurrence of PML in patients who are no longer on etrolizumab.

Specific objectives and corresponding endpoints for the study are outlined below.

Table 1 Objectives and Corresponding Endpoints for the Randomized Treatment Phase

Primary Objective	Corresponding Endpoints
• To evaluate the pharmacokinetics and pharmacodynamics of etrolizumab in a pediatric IBD patient population	• PK parameters: C_{max}, AUC_{tau}, $t_{1/2}$, C_{trough} • PD parameters: β7 receptor occupancy by flow cytometry on peripheral blood lymphocytes
Safety Objective	**Corresponding Endpoints**
• To evaluate the overall safety and tolerability of etrolizumab in pediatric population	• Incidence and severity of infection-related adverse events • Incidence of immunogenic responses (ADAs) • Incidence and severity of hypersensitivity reaction events
Exploratory Objectives	**Corresponding Endpoints**
• To evaluate additional pharmacodynamic biomarkers of etrolizumab • To evaluate clinical disease biomarkers with etrolizumab treatment • To evaluate the clinical efficacy of etrolizumab	• Changes in serum MAdCAM-1 • Changes in serum CRP and fecal calprotectin • Clinical response at Week 16, as assessed by the PUCAI (UC) and PCDAI (CD)

ADA = anti-drug antibody; AUC_{tau} = area under the concentration–time curve within a dosing interval; CD=Crohn's disease; C_{max} = maximum concentration observed; CRP = C-reactive protein; C_{trough} = steady-state concentration at the end of a dosing interval; MAdCAM-1 = mucosal vascular addressin cell adhesion molecule-1; PD = pharmacodynamic; PK = pharmacokinetic; PCDAI = Pediatric Crohn's Disease Activity Index; PUCAI = Pediatric Ulcerative Colitis Activity Index; $t_{1/2}$ =elimination half-life.

Table 2 Objectives and Corresponding Endpoints for the Open-label Extension Phase

Safety Objective	Corresponding Endpoints
• To evaluate long-term safety of etrolizumab in pediatric population	• Incidence and severity of infection-related adverse events • Incidence and severity of malignancies • Incidence of ADAs to etrolizumab • Incidence and severity of hypersensitivity reactions
Efficacy Objective	**Corresponding Endpoint**
• To evaluate long term efficacy of etrolizumab in pediatric population	• Clinical response at Week 132, as assessed by the PUCAI (UC) and PCDAI (CD)

ADA = anti-drug antibody; CD=Crohn's disease; OLE = open-label extension; PCDAI = Pediatric Crohn's Disease Activity Index; PUCAI = Pediatric Ulcerative Colitis Activity Index; UC=ulcerative colitis.

Table 3 Objectives and Corresponding Endpoints for the Progressive Multifocal Leukoencephalopathy Monitoring Phase

Safety Objective	Corresponding Endpoint
• Post-trial safety surveillance with focus on PML monitoring in patients who have stopped treatment	• Occurrence of confirmed PML events

PML = progressive multifocal leukoencephalopathy.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This pediatric PK/PD study consists of multiple phases. The randomized treatment phase is an open-label, randomized phase in which etrolizumab is administered to patients on the basis of body weight (mg/kg); randomization will be stratified by weight (< 40 kg, ≥ 40 kg). Patients will be randomized in a 1:1 ratio to receive either high-frequency etrolizumab once every 4 weeks (Q4W) or low-frequency etrolizumab once every 8 weeks (Q8W). The high-frequency dose of 1.5 mg/kg etrolizumab will be administered Q4W (Weeks 0, 4, 8, and 12). The low-frequency dose of 3.0 mg/kg etrolizumab will be administered Q8W (Weeks 0 and 8).

After the 24–week randomized treatment phase (which includes a 16–week treatment period and an 8–week safety follow-up period), patients will then have the option to participate in the 312–week OLE phase (treatment with etrolizumab 1.5 mg/kg will be administered Q4W). All patients who participate in the 24–week randomized treatment phase and the 312–week OLE phase *will enter the 12–week safety follow-up period (see Appendix 1d; no etrolizumab treatment) and will* complete *the* safety surveillance PML-monitoring phase (*see Appendix 1e;* no etrolizumab treatment *for a total of 104 weeks)*. All patients who choose not to enter the OLE phase after the 24–week randomized treatment phase will enter the 104-week PML monitoring phase.

Patients can enter the OLE phase after completion of the 24–week randomized treatment phase. If the last visit of the randomized treatment phase and Day 1 of the OLE phase occur on the same day, the assessments from the randomized treatment phase should be completed. The assessments from the randomized treatment phase can apply to the OLE assessments (i.e., the same assessments should not be repeated for the OLE).

The 104–week PML monitoring phase will consist of telephone calls approximately every 6 months (see Appendix 7) with administration of the PML Subjective Checklist. If there are any signs or symptoms suggestive of PML identified on this subjective checklist during the telephone call, the patient will be asked to come into the clinic for a neurologic examination. The PML Algorithm (see Appendix 8) will be followed for any suspected

case of PML, and any confirmed case of PML will be reported as a serious adverse event (see Section 5.4.2).

Patients who experience clinically significant worsening in their UC or CD status during the study can receive rescue therapy based on current standard of care. Patients can receive rescue therapy at any time during the study, including the treatment phase, safety follow-up phase, OLE phase and PML monitoring phase.

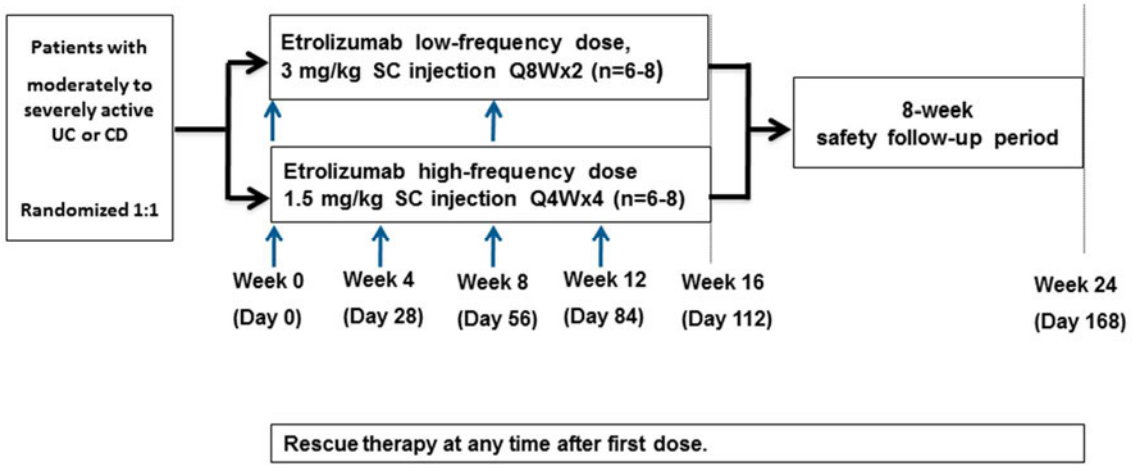
Approximately 24 pediatric patients from 4 to <18 years of age with moderate to severe UC or with moderate to severe CD will be enrolled to target at least 12 patients with evaluable PK profiles. At least 4 patients from 4 years to <12 years of age should be enrolled, which is a study obligation according to the health authority requirement. If PK and PD samples are missing, patients will be replaced at the discretion of the sponsor. Every effort should be made to collect all PK and PD samples.

Patients who initially failed screening may be rescreened twice at the discretion of the investigator.

If a patient fails any laboratory inclusion/exclusion criteria at screening, the investigator may repeat the test twice within the screening period. If the patient fails the laboratory criteria for a third time they will be considered a screen failure. It will not be considered a re-screening if blood samples have to be redrawn due to sample handling problems, breakage, or sample integrity. This multi-center study will be conducted at global sites.

The study design schemas are presented in Figure 1, Figure 2, and Figure 3.
A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema: Randomized Treatment Phase (Treatment Period and Safety Follow–up Period)

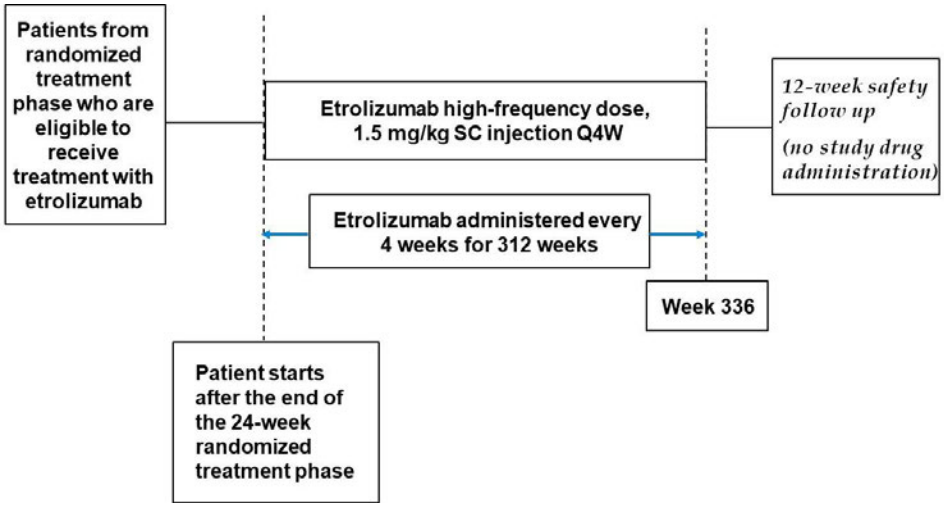


CD=Crohn's disease; OLE = open-label extension; Q4W = every 4 weeks; Q8W = every 8 weeks; UC=ulcerative colitis.

Notes: Etrolizumab dose: 1.5 mg/kg Q4W or 3 mg/kg Q8W SC injection of 0.01 mL per kg of patient weight.

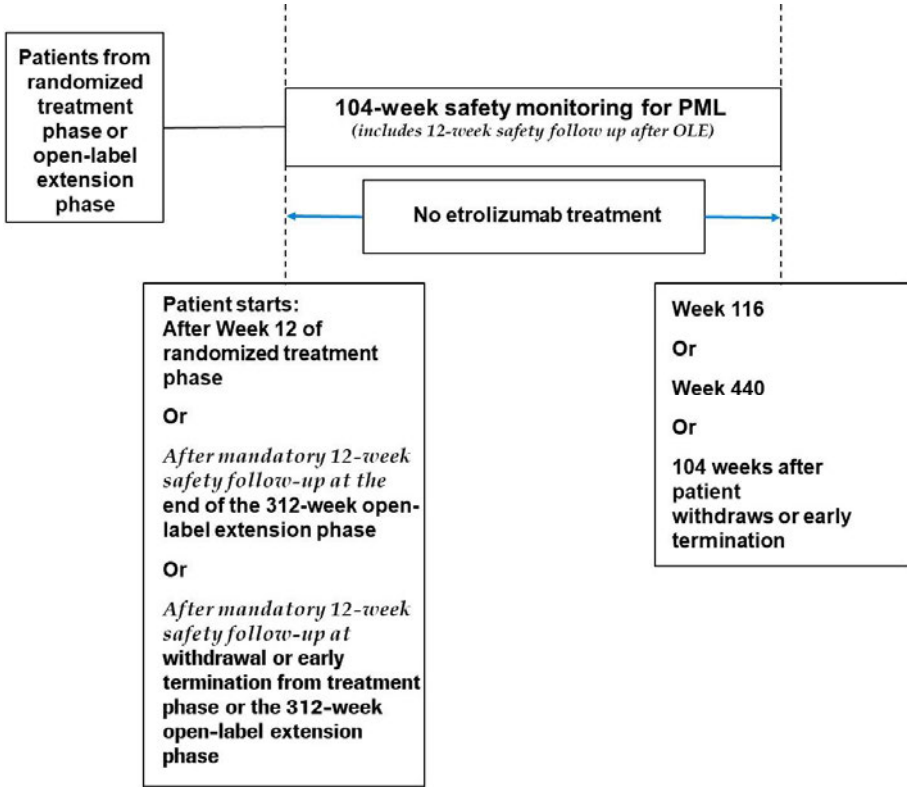
Rescue therapy prescribed based on the discretion of the investigator and disease flare, can include methotrexate, corticosteroids, immunomodulators, and excludes anti-TNFs, vedolizumab, and other biologic agents (see Section 4.4.2.2). Based on the patients disease status and physicians care practices the patient can be withdrawn from the study at any time to receive excluded therapy.

Figure 2 Study Schema: Open-label Extension Phase



Q4W = every 4 weeks; SC=subcutaneous.

Figure 3 Study Schema: Progressive Multifocal Leukoencephalopathy Monitoring Phase



OLE = open-label extension; PML = progressive multifocal leukoencephalopathy.

3.1.1 Safety Monitoring Committee

The Sponsor's Safety Monitoring Committee will assess safety on an ongoing basis. The Committee's evaluations will include, but are not limited to, adverse events, serious adverse events, and laboratory abnormalities. This committee will include a medical monitor, drug safety scientist, and biostatistician from the Sponsor. The Safety Monitoring Committee may request that additional Sponsor scientists (e.g., PK or clinical scientists) participate in data analysis.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for PK/PD or statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur 108 months after the last patient is enrolled. The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 9 years.

The randomized treatment phase will continue for 24 weeks (includes a 16–week treatment period and an 8–week safety follow-up period) after the last patient is enrolled into the study or until the Sponsor decides to terminate the study, whichever is earlier. Patients who withdraw from the treatment period should complete the 8-week safety follow-up period. All patients will enter the 104–week extended PML monitoring phase.

The OLE phase will continue for approximately 6 years after the last patient is enrolled into the study or until the Sponsor decides to terminate the study, whichever is earlier.

The PML monitoring phase will last 104 weeks for patients who enter, either from the randomized treatment phase or the OLE phase *(includes 12–week safety follow up period after completion or early discontinuation from OLE)*.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 5 years.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 9 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

Etrolizumab will be studied in children between 4 and 11 years of age and adolescents from 12 to <18 years of age. Children younger than 4 years of age will not be studied on the grounds that studies would be impossible or highly impractical due to the small number of patients in this age group and because the specific medicinal product has the potential to be unsafe in this age range of the pediatric population.

In the United States, the incidence of UC in children younger than 4 years of age is very low, with the annual incidence in this age group ranging between 0.2–0.7 per 100,000 and prevalence ranging between 1.1–2.3 per 100,000 (Herrinton et al. 2008; Abramson et al. 2010; Malaty et al. 2010). Similarly, the incidence of CD in the United States in children younger than 4 years of age is very low and presentation rarely occurs before 4 years of age (de Greef et al. 2013). Because of the small number of patients with UC and CD in children 0–4 years of age, it is impossible or highly impracticable to conduct a study in this age population. In children approximately ≥6 years of age, the functional development of the immune system and the GI tract is similar to that of adults (Holladay and Smialowicz 2000).

The nonclinical safety strategy supporting etrolizumab clinical development in children 4–17 years of age takes into consideration the age of animals in the repeat-dose toxicity studies, as well as the planned assessment of the F1 generation in the proposed prenatal/postnatal developmental study. The male animals included in the 12– and 26-week repeat-dose toxicity studies in cynomolgus monkeys were 2–4.2 years of age at study initiation (comparable to approximately 8–17 years of age in humans, with a conversion factor of 4) and were sexually immature or peripubertal as assessed by microscopic evaluation of relevant reproductive tract tissues at the end of dosing in both studies.

The female animals in the 12-week study were 2.3–3.3 years of age at study initiation (comparable to approximately 9–13 years of age in humans). Although the definitive maturity for females was not specifically captured in the microscopic evaluation of reproductive tissues in this study, the animals were likely peripubertal based on their age range. The female animals in the 26-week study were of 3.2–4.2 years of age at study initiation (comparable to approximately 13–17 years of age in humans) and did demonstrate sexual maturity at the end of the 6-month dosing phase as assessed by microscopic evaluation of relevant reproductive tract tissues.

No findings attributed to etrolizumab were identified in male and female reproductive tissues in these studies, as assessed by organ weights and macroscopic and microscopic evaluation. In the 26–week toxicity study in mice, animals were 6–7 weeks of age at study initiation and should have reached puberty before the end of study (Beckman and Feuston 2003; Marty et al. 2003). No drug-related effects were found in male or female reproductive tissues following etrolizumab administration, as assessed by organ weights and macroscopic and microscopic evaluation.

The pharmacokinetics of monoclonal antibodies in pediatric patients could be different from adults due to the difference in catabolic enzymes, changes in body composition, elimination in organs, receptor-mediated endocytosis and target receptor expression. Etrolizumab was cleared partially through the target-mediated drug disposition. The target receptor expression in pediatrics may be different from adults. The differences lead to changes in the volume of distribution, clearance, and

absorption of monoclonal antibody. Due to the complexity of the contributors involved, the direction and extent of the differences in pediatric population are not always readily predictable. The results obtained from this Phase I PK/PD study in pediatrics will provide a solid rationale for a proper dosing adjustment for pediatric population.

3.3.2 Rationale for Etrolizumab Dose and Schedule

Two dosing regimens are selected in this pediatric PK/PD study. One is 1.5 mg/kg every 4 weeks, dosed on Week 0, 4, 8, and 12, the other is 3 mg/kg every 8 weeks, dosed on Weeks 0 and 8. The rationale of the dose selection for this pediatric study is to allow evaluation of full PK and PD profiles in a pediatric population and to understand the kinetics at both linear and nonlinear concentration ranges. Two doses will allow the dose proportionality to be evaluated in a pediatric population and longer dosing interval helps to evaluate PK and PD profiles within the nonlinear concentration range.

The PK and PD (β7 receptor occupancy [RO]) profiles following SC administration of 1.5 mg/kg Q4W and 3 mg/kg Q8W were simulated by extrapolating from an adult population PK (PopPK)/PD model. The simulated median RO profile suggested that RO was fully saturated within the dosing interval across all age groups following 1.5 mg/kg Q4W. The median RO following 3 mg/kg Q8W was fully saturated most of time within the dosing interval for patients with body weight higher than 70 kg. For patients with a body weight $<$30 kg, the duration of maximum RO was about half of the dosing interval.

The simulated median C_{max} and AUCτ from patients with a body weight of 100 kg were 21.4 µg /mL and 534 µg • day/mL following 3 mg/kg Q8W. The safety of these proposed dosing regimens in pediatric population is well supported by nonclinical safety data. At the no-observed-adverse-effect-level (NOAEL) dose of 50 mg/kg SC $\times$ 27 doses in cynomolgus monkey given every week for 26 weeks (the highest dose tested), the steady-state C_{max} and $AUC_{183\text{-}190}$ were 1250 µg/mL and 9310 µg • day/mL, respectively. On the basis of the steady state C_{max} or systemic exposure (AUC), the NOAEL dose in cynomolgus monkeys provides safety factors of 58- or 17-fold, respectively, for the highest proposed dose of 3 mg/kg Q8W. Compared to the highest dose tested in humans (an LD of 420 mg SC at Week 1, and 300 mg SC at Weeks 2, 4, and 8), the safety margins for the dose of 3 mg/kg Q8W are approximately 2–fold for both C_{max} and AUCτ.

3.3.3 Rationale for PK Sampling Schedule

The sampling schedule that follows the first and last dose of etrolizumab is designed to provide sufficient data to define the critical PK and PD parameters and to understand the absorption, distribution, and elimination of this drug in a pediatric IBD population, including time to maximum observed concentration (t_{max}), clearance, and elimination half-life ($t_{1/2}$).

Considering blood draw restrictions in the pediatric population, optimized blood sampling was planned to allow determination of etrolizumab PK parameters such as AUCτ (following the last dose), C_{max} (following the first and last doses), steady-state concentration at the end of a dosing interval (i.e., just prior to next drug administration) (C_{trough}) and half-life ($t_{1/2}$) with minimal number of samples necessary. C_{max} estimates will be based on a single time point after the first and last dose where the maximum concentrations are expected based on the adult PK data. PK time points have been aligned with the proposal for the European Medicines Agency (EMA) health authority.

3.3.4 Rationale for Biomarker Assessments

Pharmacodynamic biomarkers

Pharmacodynamic biomarkers, including β7 receptors on peripheral gut homing leucocytes serum and soluble MAdCAM-1, will be measured to assess the target engagement and pharmacological effect of etrolizumab and to understand if the PK/PD relationship between etrolizumab exposure and receptor occupancy of the β7 expressing cells in the blood (and potential variability) observed in the adult UC patients are consistent with the pediatric patients with UC or CD. This will help to identify the serum concentration required for maintaining receptor occupancy in the pediatric population and to support the dose selection for Phase III pediatric clinical trial. PD sample time points have been aligned with the proposal for the EMA health authority.

Inflammatory biomarkers

All patients enrolled in the study will have fecal calprotectin and serum C-reactive protein (CRP) samples collected at the baseline (predose) and over the study period to assess the effect of etrolizumab treatment in reducing levels of inflammatory biomarkers.

Associations between exposure and these inflammatory biomarkers may also be explored.

4. MATERIALS AND METHODS

4.1 PATIENTS

A minimum of 12 patients with UC and CD from 4 years to <18 years of age will be enrolled in the study. There will be at least 4 children from 4 years to <12 years of age with evaluable PK profiles, which is a study obligation according to the health authority requirement.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form by parent or legal guardian
- Age of 4 years to <18 years at the time of signing the Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Weight of 13 kg or more

- Diagnosis of UC or CD confirmed by biopsy and established for ≥3 months (i.e., after first diagnosis by a physician according to American College of Gastroenterology [ACG] guidelines) prior to screening
- Inadequate response, loss of response or intolerance to prior immunosuppressants and/or corticosteroid treatment and/or anti-TNF therapy
- For patients with UC: moderately to severely active UC as determined by an MCS of 6–12 with an endoscopic subscore ≥2 (within the last 12 months prior to screening) and a rectal bleeding subscore ≥1
- For patients with CD: moderately to severely active CD as determined by a Pediatric Crohn's Disease Activity Index (PCDAI) score of >30 at baseline
- Must meet the following surveillance colonoscopy requirements:
  - Document evidence of surveillance for dysplasia every 1 to 2 years, beginning approximately 7 to 10 years after their initial diagnosis
- For postpubertal females of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods during the treatment period and for at least 24 weeks after the last dose of etrolizumab.

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

  Examples of acceptable contraceptive methods include bilateral tubal ligation, male sterilization, combined oral contraceptive pill or transdermal patch, spermicide and barrier [condoms], intrauterine device, implants for contraception, injections for contraception [with prolonged release], hormonal vaginal device (see Appendix 6).

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

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

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

4.1.2 Exclusion Criteria

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

4.1.2.1 Exclusion Criteria Related to Inflammatory Bowel Disease

- Prior extensive colonic resection, subtotal or total colectomy, or planned surgery
- 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
- Abdominal abscess
- A history or current evidence of colonic mucosal dysplasia
- Patients with fixed symptomatic stenosis of the intestine
- Patients with history or evidence of adenomatous colonic polyps that have not been removed.
- Patients who are not up to date on vaccinations per the local vaccine schedule will be excluded.

4.1.2.2 Exclusion Criteria Related to Ulcerative Colitis

- Severe extensive colitis per investigator judgment that colectomy is imminent OR the patient has two of the following five symptoms at screening or baseline visit:
  - 6 bowel movements daily with obvious blood
  - Abdominal examination worrisome for imminent surgery
  - Persistent fever
  - Tachycardia
  - Anemia (hemoglobin $<$ 8 g/dL)

4.1.2.3 Exclusion Criteria Related to Crohn's Disease

- Sinus tract with evidence for infection (e.g., purulent discharge) in the clinical judgment of the investigator
- Short-bowel syndrome
- Evidence of abdominal or perianal abscess
- Expected to require surgery to manage CD-related complications during the study

4.1.2.4 Exclusion Criteria Related to Prior or Concomitant Therapy

- Any prior treatment with anti-integrin agents (including natalizumab, vedolizumab, and efalizumab)
- Any prior treatment with ustekinumab
- Any prior treatment with anti-adhesion molecules (e.g., anti-MAdCAM-1)
- Any prior treatment with rituximab

- Use of IV steroids within 30 days prior to screening with the exception of a single administration of IV steroid
- Use of agents that deplete B or T cells (e.g., alemtuzumab or visilizumab) within 12 months prior to Day 1, with the exception of AZA and 6-MP
- Use of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) within 4 weeks prior to Day 1
- Use of other biologics (e.g., anti-TNF) within 8 weeks before dosing, unless drug level is below detectability before completion of the 8-week interval
- 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.)
- Apheresis (i.e., Adacolumn® apheresis) within 2 weeks prior to Day 1
- Received any investigational treatment including investigational vaccines within 12 weeks prior to Day 1 of the study or 5 half-lives of the investigational product, whichever is greater
- 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)

4.1.2.5 Exclusion Criteria Related to General Safety

- Pregnant or lactating
- Lack of peripheral venous access
- Congenital or acquired immune deficiency
- Hospitalized (other than for elective reasons) during the screening period
- Inability to comply with study protocol, in the opinion of the investigator
- Significant uncontrolled comorbidity, such as cardiac (e.g., moderate to severe heart failure New York Heart Association [NYHA] Class III/IV), pulmonary, renal, hepatic, endocrine, or GI disorders (excluding UC and CD)
- Neurological conditions or diseases that may interfere with monitoring for PML
- History of demyelinating disease
- Clinically significant abnormalities on the screening PML Subjective Checklist
- History of major neurological disorders, including stroke, multiple sclerosis, brain tumor, neurodegenerative disease, or poorly controlled epilepsy
- History of alcohol, drug, or chemical abuse $<$6 months prior to screening
- Conditions other than UC or CD that could require treatment with $>$10 mg/day of prednisone (or equivalent) during the course of the study

- Presence of metal in the body that could pose a hazard during any potential scanning in patients for whom a magnetic resonance imaging (MRI) scan is considered unsafe
- History of cancer, including hematologic malignancy, solid tumors, and carcinoma in situ, within 5 years before screening with the following caveats:
  - 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.

4.1.2.6 Exclusion Criteria Related to Infection Risk

- Congenital or acquired immune deficiency
- Patients must undergo screening for HIV and test positive for preliminary and confirmatory tests
- Positive hepatitis C virus (HCV) antibody test result, unless the patient (1) has undetectable HCV RNA levels for >6 months after completing a successful course of HCV anti-viral treatment and an undetectable HCV RNA at screening or (2) has a known history of HCV antibody positivity with a history of undetectable HCV RNA 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 is positive, the patient is not eligible for this study.
  - In the event the HBV DNA test cannot be performed, the patient is not eligible for this study.
  - If the HBV DNA test is negative, the patient is eligible for this study. These patients will undergo periodic monitoring for HBV DNA during the study.
- Positive stool test result for ova or parasites or positive stool culture for pathogens at time of screening

- Evidence of or treatment for *Clostridium difficile* (as assessed by *C. difficile* toxin testing) within 60 days prior to Day 1or 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 sample is required during screening evaluation only if clinical suspicion is high and to determine the need for CMV treatment
- History of active or latent treated TB, regardless of treatment history)
  - Patients with a history of active or latent TB (based on a positive screening assay, either purified protein derivative [PPD] skin test or QuantiFERON®-TB Gold test, 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.
- Suspicion of active TB on chest radiograph (X-ray, posteroanterior and lateral) taken within 3 months of randomization
- History of recurrent opportunistic infections and/or history of severe disseminated viral infections (e.g., herpes)
- Opportunistic infection within 3 months before screening
- 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/CD 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

4.1.2.7 Exclusion Criteria Related to Laboratory Values (at Screening)

- Serum creatinine >1.5 times upper limit of normal (ULN)
- ALT or AST >3 ULN, or alkaline phosphatase >3 ULN, or total bilirubin >2.5 ULN (unconjugated hyperbilirubinemia that is associated with known Gilbert's syndrome is not an exclusion criterion)
- In patients with diabetes*:* glycosylated hemoglobin (HbA_{1c}) > 8.0%
- Platelet count <100,000/mL

- Hemoglobin <8 g/dL
- Absolute neutrophil count <1500/mL
- Absolute lymphocyte count <500/mL

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

After written informed consent and assent have been obtained, all patients will receive a screening number, which will be assigned by an interactive voice/Web-based response system (IxRS). Following completion of the screening period and after all patient eligibility requirements are confirmed, patients will be assigned a patient number (a different number from the screening number) on Day 1 and will undergo randomization in a 1:1 ratio to receive either high-frequency dose of etrolizumab once every 4 weeks or low-frequency dose of etrolizumab once every 8 weeks. Randomization will be stratified by weight (<40 kg, ≥40 kg). A permuted blocks randomization method will be used to obtain an approximately 1:1 ratio between the two treatment arms within each stratum.

This is an open-label study, and no blinding of site, patient, or Sponsor will be implemented. The primary objective is estimation of PK and PD parameters which can be performed objectively without blinding of the dose frequency received (low vs high).

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is etrolizumab. All patients will receive etrolizumab one subcutaneous injection of 0.01 mL per kg of patient weight (1.5 mg/kg) Q4W or injection of 0.02 mL per kg of patient weight (3 mg/kg) Q8W.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Etrolizumab

F. Hoffmann-La Roche Ltd manufactures etrolizumab drug product. Etrolizumab drug product is a colorless to slightly yellow solution. The drug product is a sterile and preservative-free liquid intended for SC administration.

The drug product contains 150 mg/mL of etrolizumab in 200 mM L-arginine succinate, 20 mM L-histidine, and 0.04% (w/v) polysorbate 20, pH 5.8. Etrolizumab drug product will be provided in single-use, 3-cc glass vials that are stoppered with 13-mm fluororesin laminated stoppers and capped with aluminum seals with flip-off plastic caps.

For further details, see the etrolizumab (PRO145223, RO5490261) Investigator's Brochure.

Upon arrival of investigational products at the site, the pharmacist or designee 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.

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 that include but are not limited to the study manual and laboratory manual.

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

4.3.2 Study Treatment Dosage, Administration, and Compliance

4.3.2.1 Etrolizumab

The treatment regimens are summarized in Section 3.1.

Etrolizumab will be administered at the site during the randomized treatment phase. During the OLE phase, etrolizumab may be administered at the site.

Patients will receive treatment with etrolizumab 1.5 mg per kg patient weight SC Q4W weeks or 3 mg per kg patient weight SC Q8W. Injections will be administered to the abdomen. If the abdomen is not available for injection, the patient may receive a SC dose in the thigh. Each patient will receive one SC injection of 0.01 mL per kg patient weight or injection of 0.02 mL per kg of patient weight at each treatment visit based on the treatment regimen (the low or high frequency arm).

Etrolizumab vials are stable at 2°C−8°C (36°F−46°F). Etrolizumab vials should not be frozen or shaken and should be protected from direct sunlight.

Any overdose or incorrect administration of etrolizumab should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

Guidelines for etrolizumab treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.

Patients will be monitored for acute hypersensitivity reactions for at least 1 hour after the end of the injection. Epinephrine and parenteral diphenhydramine must be readily available for immediate use if required to treat a hypersensitivity reaction; site personnel must be able to detect and treat such reactions.

Guidelines for etrolizumab administration will be provided in supporting documents.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (etrolizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Etrolizumab

The Sponsor will offer continued access to Roche IMP etrolizumab free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMP etrolizumab after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMP etrolizumab after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for etrolizumab
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for etrolizumab
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

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

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, topical medications, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 8 weeks prior to initiation of study drug to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. The doses of these therapies do not have to be stable at the time of screening and during the study period.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy (e.g., growth hormone therapy)
- Steroids (IV, oral, or topical)
- 5-ASA (oral or topical)
- Immunosuppressants (i.e., AZA, 6-MP, or MTX)

Premedication with antihistamines, antipyretics, and/or analgesics may be administered at the discretion of the investigator.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice.

4.4.1.1 *Coronavirus Disease 2019 Vaccines*

Treatment decisions regarding the use of coronavirus disease 2019 (COVID-19) vaccines for patients eligible to receive them should be based on the physician's best clinical judgment. Based on a review of the underlying disease biology, patient population, the mechanism of action of etrolizumab, and the information available to date on COVID-19 vaccines, it is unlikely that etrolizumab will have an impact on the efficacy of currently approved COVID-19 vaccines (mRNA vaccines, inactivated vaccines, and replication deficient adenovirus vaccines) or that these currently approved vaccines will impact the safety or efficacy of etrolizumab. COVID-19 vaccines should be documented in the CRF as concomitant medication. For more detailed questions or questions about specific types of COVID-19 vaccines, please contact the Medical Monitor.

4.4.2 Cautionary Therapy

4.4.2.1 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of UC or CD may be used during the study at the discretion of the investigator.

4.4.2.2 Rescue Therapies

The worsening of UC or CD may result in the use of rescue medications, based on the discretion of the Principal investigator.

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

Rescue therapy with anti-TNF agents or their corresponding biosimilars, cyclosporine, tacrolimus, sirolimus, MMF, anti-adhesion molecules, natalizumab, vedolizumab, ustekinumab, efalizumab, rituximab, other lymphocyte depleting agents (except AZA and 6-MP), or other biological or investigational therapeutics will not be allowed in conjunction with etrolizumab because of the level of immunosuppression anticipated with the use of these agents. Patients who receive such therapies are not to receive further study treatment or enter the open-label treatment phase, and will be required to enter safety follow-up period. All patients will be offered participation in the 104–week PML monitoring phase *(includes 12–week safety follow-up period after completion or early discontinuation from OLE).*

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited during the 24–week randomized treatment phase as described below:

- Any investigational treatment or experimental therapy including investigational vaccines and biologic agents
- 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, ustekinumab, or rituximab
- Use of TNF inhibitors, including biosimilars
- Use of anakinra or abatacept and/or other biological therapeutics
- Use of *other* anti-adhesion molecules
- Use of other biologic agents

4.5 STUDY ASSESSMENTS

The Schedule of Assessments to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient.

Randomized Treatment Phase Assessments

The randomized treatment phase will consist of assessments for a 16–week treatment period and 8–week safety follow–up period, which are outlined below.

Treatment Period Assessments

Patients will be assessed for the 16–week treatment period at intervals specified in Appendix 1a.

Safety Follow-up Period Assessments

Safety follow-up will be conducted for a period of 8 weeks. Patients will be assessed for the safety follow-up period at intervals specified in Appendix 1b. The visits should be scheduled based on the date of the last dose in the treatment phase.

Following the safety follow-up period, patients will have the option to continue into the OLE phase. If the patient chooses not to continue to receive etrolizumab treatment in the OLE phase, they will be offered participation in the 104–week PML monitoring phase *(includes 12–week safety follow up period after completion or early discontinuation from OLE) as specified in Appendix 1e.* Patients will participate in 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 safety follow-up phase 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.

Open-Label Extension Phase Assessments

The OLE phase assessments will be conducted on patients that choose to participate in the OLE. Patients will be assessed at intervals specified in Appendix 1c.

PML Monitoring Phase Assessments

All patients will be offered participation in the 104-week PML monitoring phase *(which includes 12–week safety follow up period after completion or early discontinuation from OLE).* The Schedule of Assessments for the PML monitoring phase can be found in Appendix 1e.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent and minor assent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms and Assent Forms for enrolled patients and for patients who are not subsequently enrolled (e.g., screen failures, eligible patients who choose not to enroll) will be maintained at the study site.

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

4.5.2 Rescreening

If a patient does not meet all the eligibility criteria within 35 days after the original screening visit, rescreening is permitted. Patients found to be ineligible for entry into the study may be rescreened twice (e.g., if the patient develops additional manifestations of UC or CD, a worsening of existing manifestations at a later time, if patient's clinical status has changed such that the abnormal laboratory value may be directly affected [e.g., transfusion], or if there is evidence that the central laboratory sample may have degraded during transport) with the exception of certain laboratory testing (described below). Each patient must re-consent before rescreening occurs.

Rescreening is not required for the following assessments provided the results are available from the initial screening, and the date of the initial screening assessment was ≤6 weeks prior to the rescreening randomization visit.

- HIV preliminary and confirmatory tests
- HCV antibody test
- Hepatitis B assessment (i.e., surface antigen [HBsAg] core anti-body [HBcAb], and if required, HBV DNA)

If, in the investigator's judgment, the patient is deemed to have been at risk of any of the above infections (based on medical history, or geographical or social circumstance) the patient should be rescreened with the above tests.

Patients who are classified as screen failures due to the presence of *C. difficile* may be rescreened 60 days after the end of successful treatment.

As described in Section 4.5.6 if a negative TB screening test result has been documented within 3 months before screening or rescreen, no repeat test is required.

4.5.3 Medical History, Concomitant Medication, and Demographic Data

Medical history includes clinically significant diseases, procedures, and all medication taken in the 4 weeks prior to screening (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies). Demographic data, including age, sex, whether the patient is a twin sibling and self-reported race/ethnicity, will be collected during screening.

4.5.4 Physical Examinations

A complete physical examination will be performed at screening and 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 by the investigator (see Appendix 7 for PML assessment details and Appendix 8 for PML algorithm).

Clinically significant findings from the physical examination should be recorded as medical history during screening.

Symptom-driven physical examinations will be performed during the randomized treatment phase at the indicated timepoints in the Schedule of Assessments (see Appendix 1). New or worsened abnormalities from screening should be recorded as adverse events, if appropriate.

During the physical exam, Tanner stage (Appendix 5) will be assessed to determine the physical development.

During the OLE phase, a limited symptom-driven physical examination, including GI will be conducted.

4.5.5 Vital Signs

Vital signs will include measurements of heart rate and systolic and diastolic blood pressure after the patient has been in a seated position for 5 minutes, which will occur at the indicated timepoints in the Schedule of Assessments (see Appendix 1). Record vital signs before study drug administration.

Height should be measured according to the Schedule of Assessments (Appendix 1).

Weight should also be measured according to the Schedule of Assessments (Appendix 1).

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Laboratory assessments will be performed as indicated on the Schedule of Assessments (see Appendix 1). All laboratory assessments will be sent to one or more central laboratories for analysis with the exception of CMV. If there is suspicion for clinically significant CMV colitis, a colonic biopsy sample should be sent for CMV evaluation,

which may be conducted locally depending on local requirements for the timing of the test result. Urine pregnancy testing will be conducted locally.

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 $\geq$ 5 mm. Patients with a history of Bacille Calmette-Guerin (BCG) vaccination should be screened using the QuantiFERON-TB Gold test only. An indeterminate QuantiFERON-TB Gold test should be repeated. A positive QuantiFERON-TB Gold test or two successive indeterminate QuantiFERON-TB Gold test results should be considered a positive diagnostic TB test. An indeterminate QuantiFERON-TB Gold test followed by a negative QuantiFERON-TB Gold test, should be considered a negative diagnostic TB test.
  - If a negative TB screening test has been documented within 3 months of screening, no new test is needed.
- John Cunningham virus (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.
- CRP
- *C. difficile* toxin assay in stool, stool culture and sensitivity testing, stool ova and parasites analysis
- Pregnancy test: All postpubertal female patients (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 tests
  - HBV (HBsAg, total HB core antibody [anti-HBc] and HBV DNA)
  - HCV antibody
  - HCV RNA: Measurement of HCV RNA with use of the Amplicor assay is required when the patient has a known history of HCV antibody positivity with past documentation of undetectable HCV RNA, either with or without history of anti-viral treatment. Patients with newly diagnosed HCV antibody positivity are not eligible for this study and, therefore, do not require measurement of HCV RNA.
  - HIV
- PK assays
  - Serum samples will be collected for determination of etrolizumab concentrations in all patients. Samples will be analyzed using a validated assay.
- Fecal calprotectin testing
- PD biomarker assays
  - Serum samples will be collected and qualified methods will be used to measure MAdCAM-1
  - Serum samples, whole blood, and stool may be assessed for additional exploratory biomarkers
  - Whole blood will be used for flow cytometry with qualified methods to measure β-7 receptor occupancy
- Anti-drug antibody (ADA) assays
  - Serum samples will be collected for detection and characterization of antibodies against etrolizumab in all patients. Samples will be analyzed using a validated assay. For ADA samples without matched PK determinations, etrolizumab concentrations may be measured for the purpose of helping interpret ADA data. ADA samples may also be utilized for exploratory PD biomarkers.
- CMV testing of colonic biopsy sample: ONLY necessary if there is suspicion for clinically significant CMV colitis. Colon biopsy sample (to be obtained at the base of the ulcer) will be analyzed for histologic presence of CMV, but otherwise is not necessary for inclusion in the study. Analysis should be performed locally if possible or can be sent to a central laboratory if necessary.

Routine hematology and biochemistry tests can be used to satisfy inclusion/exclusion criteria if samples are collected within the 35-day window between screening and baseline. If these tests are not planned hematology and biochemistry samples should be collected at screening and analyzed accordingly.

The total volume of blood loss for laboratory assessments (including all safety, PK/PD, and efficacy samples) does not exceed the per-visit and cumulative-visit recommendations of the National Institutes of Health for the expected average weights of the patient population.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.10), biological samples will be destroyed when the final Clinical Study Report has been completed, with the exception of stool and serum samples collected for PK, PD, or immunogenicity analysis samples, which will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

4.5.7 Chest X-Ray

A chest X-ray (posteroanterior and lateral) 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.

4.5.8 Electrocardiograms

Electrocardiograms (ECG) recordings will be obtained at specified timepoints, as outlined in the Schedule of Assessments (see Appendix 1).

ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for ≥10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate.

Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to meals and any scheduled vital sign measurements and blood draws.

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

4.5.9 Clinical Outcome Assessments

Clinical outcome assessments (COAs; Pediatric Ulcerative Colitis Activity Index [PUCAI] and PCDAI) data will be collected to help characterize the treatment 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 COAs completed at the sites (PUCAI and PCDAI) should be administered at the investigational site prior to the completion of non-COA assessments

and before the patient receives any disease-status information or study drug during that visit.

COA data will be collected and assessed at visits according to the Schedule of Assessments in Appendix 1.

The sign/symptoms items of the PUCAI and PCDAI, described below, can either be completed by patients/caregivers on worksheets, or collected via interview. If the data is collected via interview, then the question and response options should be read verbatim, and the patient/caregiver response recorded.

Pediatric Ulcerative Colitis Activity Index (PUCAI)
The PUCAI quantifies the signs and symptoms of patients with UC (see Appendix 2). The components of the PUCAI include patient- or caregiver-reported abdominal pain, rectal bleeding, stool consistency, number of stools, nocturnal stools, and activity level on average over the past two days (Turner et al. 2007). These signs and symptoms are reported by patients (age ≥7 years), or caregivers of patients <7 years of age, via worksheets or an interview with the clinician, and the remaining components are completed by the physician. A numerical value is assigned to each response; responses are summed to a total score of 0-85, with a higher score indicating more severe disease. Please refer to Appendix 2 for details.

Pediatric Crohn's Disease Activity Index (PCDAI)
The PCDAI quantifies the signs and symptoms of patients with CD (see Appendix 3). The components of the PCDAI include patient- or caregiver-reported number of stools, abdominal pain, and general well-being; presence of extraintestinal manifestations; physical examination findings; height and weight, and hematocrit, erythrocyte sedimentation rate, and serum albumin over the past week (Hyams et al. 1991).
Of these components, number of soft stools, abdominal pain, and general well-being are reported by patients (age ≥7 years) or caregivers of patients < 7years of age and the remaining components are completed by the physician. A numerical value is assigned to each response; responses are summed to a total score of 0–100, with a higher score indicating more severe disease Please refer to Appendix 3 for details.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

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

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to etrolizumab or UC or CD:

- Saliva sample for exploratory analysis (first visit only)

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

Specimen types include the following (see Appendix 1 for specific collection timepoints):

- Residual Serum
- Residual Stool

Potential applications of RBR samples include, but are not limited to, assays for mRNA expression and other biomarker(s) that predict response or toxicity to etrolizumab.

Additionally, the above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing (NGS), or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.10.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

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

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

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

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

4.5.10.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

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

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Patient Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.10.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient’s safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Pregnancy
- Anaphylaxis or other severe hypersensitivity reaction
- Develop colonic mucosal dysplasia
- Malignancy (with the exception of local and resected basal or squamous cell carcinoma of the skin) or cervical Pap test with AIS, HSIL, or CIN of Grade >1

- Specific serious infection (see Section 5.1.1.1 for details on serious infection):
  - Any patient who experiences a specific de novo or reactivated serious viral infection, such as HBV, HCV, HIV, should discontinue study medication.
  - Any patient who develops life-threatening infections during the study should discontinue study medication.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Patients will return to the clinic for an early withdrawal from treatment or treatment discontinuation visit after the last dose of study drug (see Appendix 1 for additional details).

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Any medical condition the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- The 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
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

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. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will be replaced.

4.6.3 Study 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 Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

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, patients, and their caregivers 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 Associated with Etrolizumab

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

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

Important potential risks for etrolizumab include:

- Infections, in particular, serious or life-threatening infections, such as:
  - Progressive multifocal leukoencephalopathy
  - Other serious infections (e.g., gastrointestinal, opportunistic)
- Hypersensitivity reactions, in particular:
  - Anaphylactic, anaphylactoid reactions
  - Other systemic hypersensitivity reactions
- Hepatic effects
- Local injection-site reactions
- Malignancies

- Immunogenicity
- Decreased effectiveness of immunization

5.1.1.1 Serious Infections

5.1.1.1.1 Progressive Multifocal Leukoencephalopathy

Background

PML is a potentially fatal neurological condition linked to reactivation of a polyomavirus (JCV) and active viral replication in the brain. Cases of PML have been reported in patients with CD and multiple sclerosis who received concomitant treatment with the anti-α4 integrin natalizumab and immunosuppressives. Integrin α4β1, which is inhibited by natalizumab, is a pleiotropic integrin that is believed to facilitate T cell migration into the CNS. Inhibition of integrin α4β1 is thought to reduce (CNS) immune surveillance and facilitate development of PML.

According to the U.S. Package Insert for vedolizumab, which selectively impedes lymphocytes trafficking into gut tissue by specifically blocking only the α4β7 integrin and not the α4β1 integrin, one case of PML in an ENTYVIO (vedolizumab)-treated patient with multiple contributory factors has been reported in the post-marketing setting (e.g., HIV infection with a CD4 count of 300 cells/mm³ and prior and concomitant immunosuppression) to date. Although unlikely, a risk of PML cannot be ruled out.

Etrolizumab targets cells expressing the β7 integrin (α4β7 and αEβ7 cells) and not α4β1 cells. Despite the lack of theoretical or experimental evidence for a specific role of β7 integrins in leukocyte homing to the CNS and given the observation of PML risk with natalizumab, the Sponsor will continue to conduct extensive risk-monitoring procedures during this study. There have been no cases of PML in patients treated with etrolizumab.

Screening, Patient Selection, and PML Education

No known interventions can reliably prevent or treat PML if it occurs; therefore, it is important to exclude patients with a perceived higher baseline risk for PML, such as patients who have received natalizumab, efalizumab, rituximab, B or T cell depleting agents (e.g., alemtuzumab or visilizumab), with the exception of AZA and 6-MP, cyclosporine, tacrolimus, sirolimus, or MMF. Patients with a history of PML or neurological symptoms where suspected PML has not been ruled out are not eligible for this study (see Section 4.1.2).

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.

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

See Appendix 1 for details of assessments regarding PML.

PML Monitoring

During the study, patients should be closely monitored for any signs and symptoms of PML via regular subjective tests employing the use of the PML Subjective Checklist to assess the patient's mental and neurological status; see Appendix 7 for details of assessments regarding PML.

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

If a patient has a clinically significant positive finding on the PML Subjective Checklist the event should be expeditiously reported to the sponsor as adverse events of special interest or serious adverse events, as appropriate, within 24 hours (see Section 5.1.1 and Appendix 8 for the Algorithm for Evaluation of PML).

If PML is suspected, dosing with study drug 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 cerebrospinal fluid (CSF) analysis for JCV by polymerase chain reaction (PCR). If JCV is detected, the patient should be treated as a PML case and the patient should permanently discontinue study drug and enter safety follow-up.

Dosing with study drug can only be resumed in patients where PML has been ruled out. Refer to Appendix 8 for the Algorithm for Evaluation of Progressive Multifocal Leukoencephalopathy.

PML Treatment

There is no known effective treatment for PML. Plasmapheresis has been employed in some patients in an effort to promote clearance of a suspected causative agent (Tan et al. 2011). If an event of PML occurs, subsequent management of PML will be at the direction of the consulting neurologist.

Additional information for the management of this potential risk is provided in Appendix 7 (Worksheet for the PML Neurologic Examination) and Appendix 8 (Algorithm for the Evaluation of PML).

5.1.1.1.2 Other Serious Infections

Background

From an overall review of safety data from completed etrolizumab UC clinical trials, no other safety concerns have been identified for etrolizumab in terms of infections to date, besides appendicitis. Nonetheless, serious infections are a potential risk because of the mechanism of action of etrolizumab, which blocks trafficking of gut-selective lymphocytes.

Patient Selection

Patients who experienced a life-threatening infection or a de novo or reactivated serious viral infection, such as HBV, HCV, or HIV, are not eligible for this study (see Section 4.1.2).

Patients who have an ongoing serious infection event should not receive study drug until the event has completely resolved and treatment with anti-infective medications has been completed. Patients with hepatitis B infection who test positive only for core antibody (anti-HBc+) and test negative for HBV DNA test are eligible for the study; however, these patients must undergo periodic monitoring for HBV DNA during the study.

Patients with active or latent TB (not including patients who have prior vaccination with BCG will be excluded from the study. Any immunosuppressed patient with a strong suspicion of TB exposure and no prior vaccination with BCG should be considered at risk for having latent TB infection.

Patients at risk for TB exposure include:

- Patients who have household contact with a person with active TB
- Patients living in areas with high incidence of TB
- Patients who frequently visit areas with high prevalence of active TB
- Patients who meet these criteria should be evaluated per local practice to exclude latent TB.

Education, Monitoring, and Management

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

Patients who experience a serious infection event should not receive further study drug until the event has completely resolved and treatment with anti-infective medications has been completed. All efforts should be made to identify the infectious agent. Patients who develop life-threatening infections, including de novo or reactivated serious viral infection, such as HBV, HCV, HIV, during the study should discontinue study drug.

5.1.1.2 Hypersensitivity Reactions

Background

An overall review of safety data from completed studies in UC identified a very small number of hypersensitivity reactions reported in patients receiving etrolizumab, all of which were mild or moderate in severity. No anaphylactic, anaphylactoid, or severe hypersensitivity reactions have been identified for etrolizumab to date.

Anaphylaxis and hypersensitivity reactions will be closely monitored during the study.

Patient Selection

Patients who have a history of moderate or severe allergic or anaphylactic/anaphylactoid reactions to chimeric, human, or humanized antibodies, fusion proteins, or murine proteins or hypersensitivity to etrolizumab (active drug substance) or any of the excipients (L-histidine, L-arginine, succinic acid, polysorbate 20) are not eligible for this study.

Education, Monitoring, and Management

After each injection administered in the treatment phase and after the first four injections in the OLE phase, the patient must be monitored for 60 minutes for any possible hypersensitivity reaction. Medicinal products for the treatment of hypersensitivity reactions (e.g., epinephrine, antihistamines, and glucocorticoids) must be available for immediate use in the clinic for the event of an allergic reaction during administration of the study drug. Resuscitation equipment should also be available.

Patients and their caregivers should be instructed to recognize the symptoms of any anaphylactic, anaphylactoid, or hypersensitivity reaction and to contact a health care provider (HCP) or seek immediate care in case of any such symptoms. Patients are to be provided with alert cards to remind them and a caregiver or partner of the above. Please see Appendix 9 for diagnosing anaphylaxis.

Patients with symptoms of anaphylaxis or with severe hypersensitivity reactions (e.g., stridor, angioedema, life-threatening change in vital signs) must be permanently withdrawn from study drug treatment. These patients will not be eligible to receive open-label etrolizumab but are required to enter the safety follow-up phase, and offered participation in the PML monitoring phase.

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).

5.1.1.3 Hepatic Effects

Background

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

indicating liver toxicity with etrolizumab were observed. The risk in humans is currently unknown.

From an overall review of safety data from completed studies in UC, there have been no cases of potential drug-induced liver injury that have been attributed to etrolizumab.

Patient Selection

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

Education, Monitoring, and Management

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

5.1.1.4 Local Injection-Site Reactions

Background

A local injection-site reaction is any local reaction occurring at the site of injection following study drug administration.

From an overall review of safety data from completed UC studies, injection-site reactions were low in number in etrolizumab-treated patients, and all were non-serious and mild or moderate in severity.

Monitoring

In the clinic setting, patients should be monitored for signs of injection-site reactions in the period immediately following injections.

5.1.1.5 Malignancies

Background

From an overall review of safety data from completed studies in UC, the number of malignancies reported were small and no specific pattern in the types of malignancies reported or in the time to onset since the first dose of etrolizumab was noted.

Nonetheless, given the elevated risk of malignancy in this patient population a priori, the trial includes selection criteria and additional information to minimize any hypothetical risk.

Patient Selection

Patients who have a history of cancer within 5 years prior to screening (with the exception of local resected basal or squamous cell carcinoma of the skin), including AIS, HSIL, or CIN of Grade >1 or colonic dysplasia, are to be excluded from the study.

Monitoring and Management

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

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

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

5.1.1.6 Immunogenicity

Background

As with administration of any exogenous protein, a potential exists for the development of ADAs. Such antibodies can be neutralizing, with potential for reducing therapeutic effect of the drug, and/or sensitizing, with potential for eliciting allergic reactions. On the basis of the clinical experience to date, approximately 5% of patients develop ADAs to etrolizumab. *Overall, the presence of ADAs had no impact on the safety of etrolizumab-treated patients.*

Monitoring

To assess for the potential development of immunogenicity, ADA samples will be obtained at Day 1, at regular intervals during treatment, and during the Safety Follow-Up Period (Appendix 1a, Appendix 1b, and Appendix 1c) and stored appropriately for further evaluation as needed.

5.1.1.7 Decreased Effectiveness of Immunizations

Background

The effect of etrolizumab upon the efficacy of vaccinations is unknown. Whenever possible, necessary vaccinations should be performed at a minimum of 4 weeks prior to participating in a clinical trial with etrolizumab. Live attenuated vaccines should be administered at least 4 weeks prior to administration of etrolizumab and should not be administered for the duration of the clinical trial or for at least 2.5 months (approximately 5 half-lives) after final study drug administration (see Etrolizumab Investigators Brochure for reference).

These recommendations are in line with the most recent vedolizumab (ENTYVIO®) label according to which there are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVIO. In a placebo-controlled study of healthy volunteers, 61 subjects were given a single ENTYVIO 750 mg dose (2.5 times the recommended dose), and 62 subjects received placebo followed by intramuscular

vaccination with Hepatitis B surface antigen and oral cholera vaccine.
After intramuscular vaccination with three doses of recombinant Hepatitis B surface antigen, those treated with ENTYVIO did not have lower rates of protective immunity to Hepatitis B virus. However, those exposed to ENTYVIO did have lower seroconversion rates and anti-cholera titers relative to placebo after receiving the two doses of a killed, oral cholera vaccine. The impact on other oral vaccines and on nasal vaccines in patients is unknown.

5.1.1.8 Risks Associated with Worsening of Ulcerative Colitis and Crohn's Disease

Medical occurrences or symptoms of deterioration that are anticipated as part of ulcerative colitis or Crohn's disease 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. Refer to Section 4.4.2.2 for acceptable rescue therapies.

5.1.2 Management of Patients Who Experience Specific Adverse Events.

5.1.2.1 Management Guidelines

Guidelines for management of specific adverse events are outlined in Table 4. Additional guidelines are provided in the subsections below.

Table 4 Guidelines for Management of Patients Who Experience 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.

Table 4 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Signs and symptoms of possible PML	• If a patient has a positive finding on the PML Subjective 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 8). 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 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 5.4). • 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) • Sensory deficits, including sensory loss (paresthesias) • 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.

Table 4 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
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. • 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 5.4). Significant hepatic events should be evaluated promptly and managed accordingly.

Table 4 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Hypersensitivity reactions	*An overall review of safety data from completed studies in UC identified a very small number of hypersensitivity reactions reported in patients receiving etrolizumab, all of which were mild or moderate in severity. No anaphylactic, anaphylactoid, or severe hypersensitivity reactions have been identified for etrolizumab to date. 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. • All injections will be administered in the clinic. After each injection administered in the treatment phase and after the first four injections in the OLE phase, the patient must be monitored for 60 minutes. 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 9). • 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 5.4). • Medicinal products for the treatment of hypersensitivity reactions (e.g., epinephrine, antihistamines, and glucocorticoids) must be available for immediate use in the clinic for the event of an allergic reaction during administration of the study medication. Resuscitation equipment should also be available. • 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. • If etrolizumab is administered at home by a nursing professional the patient will be advised to seek emergency care in response to any potential symptom of hypersensitivity. 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 5.4.2) or non-serious (see Section 5.3.1).
Injection reactions	In the clinic setting, patients will be monitored for signs of injection site reactions in the period immediately following injections.

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

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

According to the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.10 and Section 5.3.5.11 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
  - This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs patient hospitalization (see Section 5.3.5.12)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8)
- Suspected transmission of an infectious agent by the study drug, as defined below
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Adverse events of special interest specific to etrolizumab:
  - Systemic hypersensitivity reactions and anaphylactic and anaphylactoid reactions (see Section 5.1.1.2 and Sampson's Criteria in Appendix 9)

- Neurological signs, symptoms, and adverse events that may suggest possible progressive multifocal leukoencephalopathy, on the basis of a positive finding on the PML Subjective Checklist or if there is strong clinical suspicion for progressive multifocal leukoencephalopathy (see Appendix 7 and Section 5.1.1.1.1)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4 – 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 biopsies, 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 will be reported regardless of relationship to study drug, up until the patient completes his or her last study visit (in the Safety Follow-Up Phase) or 12-weeks after the last study drug administration whichever is longer. After the Safety Follow-Up Phase, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6). 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).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

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

"How have you (or your child) felt since your last clinic visit?"

"Have you (or your child) 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 current version of the NCI CTCAE will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

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

Table 6 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 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 captured on the Adverse Event eCRF as individual signs (e.g., erythema at injection site, induration at injection site, and swelling at injection site as separate events) or symptoms (e.g., pain at injection site and pruritus at injection site as separate events) rather than a diagnosis of allergic reaction or injection-site reaction.

5.3.5.2 Worsening Ulcerative Colitis and Crohn's Disease

When recording an unanticipated worsening ulcerative colitis or Crohn's disease 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 Crohn's disease" or "worsening of ulcerative colitis or Crohn's disease").

5.3.5.3 Diagnosis versus Signs and Symptoms

For adverse events other than injection site reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.4 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.5 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.6 Abnormal Laboratory Values

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

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory

abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens. (See Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.7 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.8 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.3) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.9 Deaths

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

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 or CD, "ulcerative colitis or Crohn's disease progression" should be recorded on the Adverse Event eCRF.

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

5.3.5.10 Preexisting Medical Conditions

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

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

5.3.5.11 Lack of Efficacy or Worsening of Ulcerative Colitis or Crohn's Disease

Medical occurrences or symptoms of deterioration that are anticipated as part of ulcerative colitis or Crohn's disease 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 of ulcerative colitis or Crohn's disease on the Adverse Event eCRF, it is important to

convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of ulcerative colitis or Crohn's disease").

5.3.5.12 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

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

- 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 experienced an adverse event.

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

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

5.3.5.13 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness 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).

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

5.3.5.14 Clinical Outcomes Assessment Data

Adverse event reports will not be derived from COA data by the Sponsor, and safety analyses will not be performed using COA data. However, if any COA responses suggestive of a possible adverse event are identified during site review of the COA data,

the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

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

F. Hoffmann-La Roche Medical Monitor contact information:

Medical Monitor: [redacted], M.D. (Primary)
Telephone No.: [redacted] *(United States)*
Mobile Telephone No.: [redacted] *(United States)*

Medical Monitor: [redacted], M.D. (Secondary)
Primary Telephone No.: [redacted] (United States)
Mobile Telephone No.: [redacted] (United States)

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 12 weeks after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

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

Instructions for reporting serious adverse events that occur more than 12 weeks after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed *through the Informed Consent Form* to immediately inform the investigator if they become pregnant during the study or within 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 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. *The investigator should report the pregnancy on the* paper Clinical Trial Pregnancy Reporting Form *and submit the form* to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), 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 Clinical Trial Pregnancy Reporting Form *with additional* information on the *pregnant partner and the* course and outcome of the pregnancy *as it* becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Congenital Anomalies/Birth Defects and Abortions

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

5.4.4 Reporting Requirements for Vial and Syringe Complaints/Events

In this study, the vial and syringe are considered a medical device. The investigator must report all medical device complaints to the Sponsor. The investigator should document as much information as possible on the PD 103IMP Deviation Form, including

the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). The PD103 IMP deviation form, together with pictures of the defective vial and syringe, should be sent to *kaiseraugst.global_impcomplaint_management@roche.com.*

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

If the medical device (vial and syringe) results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2. If the medical device results in an adverse event to an individual other than the study patient, the device complaint must be reported on the PD103 form and the adverse event must be reported as a spontaneous adverse event to the Sponsor.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 12 weeks after the last dose of study drug, see Section 5.3.1) if the event is 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

progressive multifocal leukoencephalopathy, regardless of relationship to study drug, for up to 2 years after the patient's last dose of study drug. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number 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 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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary analysis of the study will be performed when all the data from the randomized controlled part of the study are in the database and has been cleaned and verified.

6.1 DETERMINATION OF SAMPLE SIZE

A sample size of 12–16 patients has been considered sufficient in order to evaluate the PK and PD endpoints. No formal sample size and power calculations were performed.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized.

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

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics such as age, sex, race, duration of disease, disease activity scores, prior anti-TNF use, concomitant corticosteroids or immunosuppressant use will be summarized by means of descriptive statistics, and presented overall and by dose regimen.

6.4 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients with sufficient data to enable estimation of key parameters such as AUC (area under the curve), C_{max} (maximum concentration), C_{trough} (trough concentration) and $t_{1/2}$ (elimination half-life).

Non-compartmental analysis will be used to derive PK parameters including C_{max} and T_{max} after the first and final dose, $t_{1/2}$, AUC within dosing interval (AUC_{84-112}) and (AUC_{56-112}) for 1.5 mg/kg Q4W and 3 mg/kg Q8W, respectively.

All PK parameters will be listed and summarized by descriptive summary statistics including means, geometric means, ranges, standard deviations, and coefficients of variation.

Individual and mean concentration versus time data will be tabulated and plotted by dose level.

PK data from this study may be combined with data from the adult study to perform a population PK analysis. Population typical value of PK parameters will be estimated for the entire study population, along with estimates of intra- and inter-patient variance and an estimate of random error. Individual patient parameter estimates will be computed using the post hoc analysis procedure. A prospective analysis plan will be prepared, and the population PK analysis will be presented in a report separate from the Clinical Study Report of this study.

Additional exploratory PK/PD analyses or modeling may be conducted as appropriate.

6.5 PHARMACODYNAMIC ANALYSES

All PD parameters will be listed and summarized by descriptive summary statistics including means, standard deviations, medians, ranges, and coefficients of variation.

6.6 SAFETY ANALYSES

The safety analysis population will consist of all patients who received at least one dose of study drug, with patients grouped according to dose regimen received.

Safety will be assessed through descriptive summaries of adverse events (including serious adverse events, malignancies, infections – in particular GI infections, systemic hypersensitivity events, and injection site reactions), laboratory test results, and vital signs.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after etrolizumab treatment (post-treatment incidence) will be summarized by treatment group. When determining post treatment incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but developed an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and PD endpoints will be assessed and reported via descriptive statistics.

6.8 BIOMARKER ANALYSES

Beta-7 receptor occupancy and serum MAdCAM-1 results will be summarized by dosing group and timepoints as absolute values and/or change from baseline. Summary statistics may be provided.

A PK/PD model may be developed to evaluate the PK/PD relationship after combining data from adult's study. This modeling work will be reported separately outside the Clinical Study Report of this study.

6.9 EXPLORATORY ANALYSES

PUCAI/PCDAI response or remission rates will be summarized descriptively over time within each treatment group. Disease activity scores and subscores, fecal calprotectin levels and serum CRP levels and their change from baseline will also be summarized descriptively over time to assess the efficacy of etrolizumab in reducing signs and symptoms of disease and levels of inflammatory biomarkers.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

COA data will be collected on paper questionnaires that may be administered via interview with the clinician. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated

instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form) will be provided to each site.
If applicable, it will be provided in a certified translation of the local language.
The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

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 (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5)

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures,

prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 20 sites globally will participate to enroll approximately 24 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

A Safety Monitoring Committee will be employed to monitor and evaluate patient safety throughout the study.

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 *Study Information* at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1a
Schedule of Assessments: Randomized Treatment Phase (Treatment Period)

Assessments	Screening Day [b] – 35 to – 0	Study Days (±3 days) [a]											
		1 [c]	4	28 (Wk 4)	56 (Wk 8)	60 [d]	70 [d]	84 (Wk 12)	88	98	112 (Wk 16)	Unscheduled Visit [e]	Early Withdrawal from Treatment or Discontinuation
Informed consent	x												
Review eligibility criteria	x	x [f]											
Demographic data	x												
Pregnancy test [g]	x	x [f]		x [f]	x [f]			x [f]			x		x
Vital signs (BP and pulse)	x	x [f]	x	x [f]	x [f]			x [f]	x	x	x	x	x
ECG	x												x
Chest X-ray [h]	x												
Height	x	x		x	x			x			x	x	x
Weight	x	x		x	x			x			x	x	x
Tanner Stage	x												x
Medical history	x												
Physical examination [i]	x							x		x		x	x
PML neurologic examination [j]	x		x					x				x [e]	x
Hematology	x	x [f]		x	x [f]			x		x	x	x [e]	x [l]
ESR [k]	x			x	x			x			x	x	x
Chemistry	x	x [f]		x [k]	x [f]			x [k]		x	x	x [e]	x [l]
Urinalysis	x	x [f]			x [f]							x [e]	

Appendix 1a
Schedule of Activities: Randomized Treatment Phase (Treatment Period) (cont.)

Assessments	Screening Day [b] – 35 to – 0	Study Days (±3 days) [a]											
		1 [c]	4	28 (Wk 4)	56 (Wk 8)	60 [d]	70 [d]	84 (Wk 12)	88	98	112 (Wk 16)	Unscheduled Visit [e]	Early Withdrawal from Treatment or Discontinuation
TB screen [m]	x												
Viral serology and detection tests [n]	x												
Saliva sample [o]		x											
Stool sample	x [p]	x [q]									x [q]		x [q]
PK sampling (serum) [r]		x	x	x	x	x	x	x	x	x	x	x [e]	x [l]
Anti-drug antibody sample (serum) [r,s]		x		x				x			x	x [e]	x [l]
Plasma sample (storage for post-study JCV antibody testing) [t]	x												
PUCAI or PCDAI [u]		x		x	x			x			x	x [e]	x [l]
Serum sample (CRP)		x [f]		x [f]							x	x [e]	x [l]
PD (receptor occupancy) flow cytometry sampling (whole blood) [r]		x	x		x			x		x	x	x	x
Serum PD measures (MAdCAM-1) [r]		x	x		x			x		x	x	x	x
Colonic biopsy (CMV, if required)	x [v]											x [e]	

Appendix 1a
Schedule of Activities: Randomized Treatment Phase (Treatment Period) (cont.)

Assessments	Screening Day [b] – 35 to – 0	Study Days (±3 days) [a]											
		1 [c]	4	28 (Wk 4)	56 (Wk 8)	60 [d]	70 [d]	84 (Wk 12)	88	98	112 (Wk 16)	Unscheduled Visit [e]	Early Withdrawal from Treatment or Discontinuation
Concomitant medications		x	x	x	x			x	x	x	x	x	x
Adverse events	x	x	x	x	x			x	x	x	x	x	x
Randomization		x [w]											
Etrolizumab administration Q4W [a, x]		x		x	x			x					
Etrolizumab administration Q8W [a, x]		x			x								

ADA = anti-drug antibody; BP = blood pressure; CD = Crohn's Disease; CMV = cytomegalovirus; CRP = C-reactive protein; ECG = electrocardiogram; eCRF = electronic Case Report Form; ESR = erythrocyte sedimentation rate; HBc = HBV core antibody total; HBsAg = HBV surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; JCV = John Cunningham virus; MAdCAM-1 = mucosal vascular addressin cell adhesion molecule-1; MCS = Mayo Clinic Score; PD = pharmacodynamics; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy; PCDAI = Pediatric Crohn's Disease Activity Index; PUCAI = Pediatric Ulcerative Colitis Activity Index; Q4W = every 4 weeks; Q8W = every 8 weeks; TB = tuberculosis; UC = Ulcerative Colitis; Wk = week.

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

[a] The time window for days etrolizumab is administered is ±1 day.

[b] All assessments must be performed after obtaining informed consent.

[c] Day 1 of Week 0.

[d] These samples are only collected for patients receiving 3 mg/kg etrolizumab administration Q8W.

Appendix 1a
Schedule of Activities: Randomized Treatment Phase (Treatment Period) (cont.)

[e] Conducted at the discretion of the investigator. Unscheduled visit represents a visit that is not per the 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 should be symptom driven (e.g., only perform PML neurologic examination if patient reports symptoms suspected of PML; for disease worsening, infectious etiologies may be investigated if clinically indicated; and confirmation of clinical relapse is performed by the MCS assessment). Assessments corresponding to items noted in this column should be recorded on the eCRF.

[f] On days etrolizumab is administered, perform prior to administration.

[g] Administer a serum pregnancy test at screening for all postpubertal female patients. A urine test may be performed at other specified visits; however, if the urine test result is positive, a confirmatory serum test must be performed. Patients must be reminded throughout the study that that in case of a positive pregnancy test, administration of study drug will be stopped immediately. Do not administer etrolizumab unless the serum pregnancy test result is negative. A urine pregnancy test is only required in female patients at Tanner Stage 2 or greater, or after onset of menarche. The test must be performed on a fresh voided sample.

[h] Not required if patient has a normal chest X–ray result within 3 months prior to screening.

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

[j] PML neurologic examination consists of the PML Subjective Checklist. Administer before other assessments, per Appendix 7.

[k] For patients with Crohn's disease only. Hematocrit, albumin, and erythrocyte sedimentation rate (ESR) will be collected to calculate the PCDAI score.

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

[m] 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).

[n] Viral serology and detection tests include HIV test, hepatitis B and C serology, hepatitis B DNA and hepatitis C RNA (Amplicor). Patients must undergo screening for HBV and HCV. This includes testing for HBsAg, anti-HBc, and hepatitis C antibody. Enrolled patients who are hepatitis B core antibody positive should have hepatitis B DNA measured at these timepoints. 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] Will be retained in the Research Biosample Repository for possible genetic analysis.

[p] Samples will be used for fecal calprotectin assay and culture and sensitivity testing; ova, parasites, and *Clostridium difficile* toxin testing.

[q] Samples will be used for, but not limited to, fecal calprotectin and microbiota analysis.

[r] On days that etrolizumab is administered, sample should be taken prior to administration. If no ADA sample is specified for a visit, a PK sample may be used for ADA analysis.

Appendix 1a
Schedule of Activities: Randomized Treatment Phase (Treatment Period) (cont.)

[s] If serum sickness or a clinically significant allergic drug reaction is suspected, the Sponsor should be notified, and serum for etrolizumab level and ADAs should be drawn and sent to the central laboratory. ADA samples may also be utilized for exploratory PD assessments or assessment of drug concentrations.

[t] 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.

[u] PUCAI and PCDAI should be calculated prior to randomization. For children who are 6 years of age or younger, the parent or caregiver can respond to the questions on the patient's behalf.

[v] IF REQUIRED: Only if there is suspicion for clinically significant CMV colitis, one biopsy sample should be obtained from the base of the ulcer to evaluate for histological presence of CMV. Analysis should be performed locally if possible, or can be sent to a central laboratory if necessary. Result must be negative for CMV prior to dosing on Day 0.

[w] Randomization to occur prior to first dose at Day 0.

[x] Patients will be randomized in a 1:1 ratio to receive either high-frequency dose of etrolizumab once every 4 weeks or low-frequency dose of etrolizumab once every 8 weeks. The high-frequency dose of 1.5 mg/kg etrolizumab will be administered once every 4 weeks at Weeks 0, 4, 8, and 12. The low-frequency dose of 3 mg/kg etrolizumab will be administered once every 8 weeks at Weeks 0 and 8.

Appendix 1b
Schedule of Assessments: Randomized Treatment Phase (Safety Follow-up Period)

Assessments	Week (±3 days)			Unscheduled Visit [b]
	Week 18	Week 20	Week 24 or Early Withdrawal Visit [a]	
Concomitant medications	x	x	x	x
Adverse events	x	x	x	x
ECG			x	
Urine pregnancy test [c]			x	
Physical examination		x	x	x
PD (receptor occupancy), flow cytometry sampling (whole blood) [d]	x	x	x	
Serum PD measures (MAdCAM-1) [d]	x	x	x	
PK sampling (serum) [d]	x	x	x	
Anti-drug antibody sample (serum) [e, f]			x	
PML neurologic examination [g]		x	x	x

Appendix 1b
Schedule of Assessments: Randomized Treatment Phase (Safety Follow-up Period) (cont.)

ADA = anti-drug antibody; ECG = electrocardiogram; MAdCAM-1 = mucosal vascular addressin cell adhesion molecule-1; PD = pharmacodynamic; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy.

[a] All assessments indicated for the Early Withdrawal Visit should be performed if the patient discontinues prior to completion of the 8-week safety follow-up period.

[b] Unscheduled visit for safety monitoring.

[c] A urine test may be performed; however, if urine test result is positive, a confirmatory serum test must be performed. A urine pregnancy test is only required in female patients at Tanner Stage 2 or greater, or after onset of menarche. The test must be performed on a fresh voided sample.

[d] PD and PK samples will be collected at Days 126 (Week 18), 140 (Week 20) and 168 (Week 24).

[e] If serum sickness or a clinically significant allergic drug reaction is suspected, the Sponsor should be notified and serum for *the analysis of study drug level* and ADAs should be drawn and sent to the central laboratory. ADA samples may be used for PK and/or exploratory PD assessments.

[f] ADA samples only need to be taken on Week 24 and at the Early Withdrawal Visit.

[g] PML neurologic examination consists of the PML Subjective Checklist. Administer before other assessments as per Appendix 7.

Appendix 1c
Schedule of Assessments: Open-Label Extension Phase

Clinic Visits Week 0–Week 44

	Etrolizumab Administration Every 4 Weeks											
	Clinic Visit Starting at Day 1 of Week 0 (± 3 days)											
Assessments	0 [a,b]	4	8	12	16	20	24	28	32	36	40	44
Vital signs (BP, pulse rate)	x			x			x			x		
ECG	x											
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x
Height	x	x	x	x			x			x		
Weight	x	x	x	x	x	x	x	x	x	x	x	x
Tanner Stage	x											
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x
Limited symptom driven physical examination, including GI	x	x		x			x			x		
PML neurologic examination [e]	x			x			x			x		
PUCAI and PCDAI [f]		x	x	x			x			x		
Pregnancy test [g]	x	x	x	x	*x*	*x*	x	*x*	*x*	x	*x*	*x*
Hematology	x	x [h]	x [h]	x			x			x		
ESR [h]		x	x	x			x			x		

Appendix 1c
Schedule of Assessments: Open-Label Extension Phase (cont.)

Clinic Visits Week 0–Week 44 (cont.)

	Etrolizumab Administration Every 4 Weeks											
	Clinic Visit Starting at Day 1 of Week 0 (± 3 days)											
Assessments	0 [a,b]	4	8	12	16	20	24	28	32	36	40	44
Chemistry	x	x h	x h	x			x			x		
Hepatitis B DNA [i]	x			x			x			x		
Serum sample (CRP)	x											
Etrolizumab PK sample (serum) [j]	x			x								
Anti-drug antibody sample (serum) [j, k]	x			x								
Etrolizumab administration	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1c
Schedule of Assessments: Open-Label Extension Phase (cont.)

Clinic Visits Week 48-Week 92

	Etrolizumab Administration Every 4 Weeks											
	Clinic Visit (± 7 days)	Clinic Visit (± 3 days)										
Assessments	48	52	56	60	64	68	72	76	80	84	88	92
Vital signs (BP, pulse rate)	x			x			x			x		
ECG	x											
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x
Height	x			x			x			x		
Weight	x	x	x	x	x	x	x	x	x	x	x	x
Tanner Stage												
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x
Limited symptom driven physical examination, including GI	x			x			x			x		
PML neurologic examination [e]	x			x			x			x		
PUCAI and PCDAI [f]	x			x			x			x		
Pregnancy test [g]	x	*x*	*x*	x	*x*	*x*	x	*x*	*x*	x	*x*	*x*
Hematology	x			x			x			x		

Appendix 1c
Schedule of Assessments: Open-Label Extension Phase (cont.)

Clinic Visits Week 48-Week 92 (cont.)

	Etrolizumab Administration Every 4 Weeks											
	Clinic Visit (± 7 days)	Clinic Visit (± 3 days)										
Assessments	48	52	56	60	64	68	72	76	80	84	88	92
ESR [h]	x			x			x			x		
Chemistry	x			x			x			x		
Hepatitis B DNA [i]	x			x			x			x		
Serum sample (CRP)	x											
Etrolizumab PK sample (serum) [j]	x											
Anti-drug antibody sample (serum) [j, k]	x											
Etrolizumab administration	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1c
Schedule of Assessments: Open-Label Extension Phase (cont.)

Clinic Visits Week 96–Week 312, Unscheduled, and Early Withdrawal from Treatment

Assessments	Clinic Visit (± 7 days) Weeks 96, 120, 144, 168, 192, 216, 240, 264, 288	Clinic Visit (± 3 days) Weeks 100, 104 , 112, 116, 124, 128, 136, 140, 148, 152, 160, 164, 172, 176, 184, 188, 196, 200, 208, 212, 220, 224, 232, 236, 244, 248, 256, 260, 268, 272, 280, 284, 292, 296, 304, 308	Clinic Visit (± 3 days) Weeks 108, 132, 156, 180, 204, 228, 252, 276, 300	Clinic Visit (–14 days) Week 312	Unscheduled Visit [c]	Early Withdrawal from Treatment Visit [d]
Vital signs (BP, pulse rate)	x		x	x		x
ECG	x		x			x
Concomitant medications	x	x	x	x	x	x
Height	x		x	x	x	x
Weight	x	x	x	x	x	x
Tanner Stage	x		x	x	x	x
Adverse events	x	x	x	x	x	x
Limited symptom driven physical examination, including GI	x		x	x	x	x
PML neurologic examination [e]	x		x	x	x [c]	x
PUCAI and PCDAI [f]	x		x	x	x [c]	x

Appendix 1c
Schedule of Assessments: Open-Label Extension Phase (cont.)

Clinic Visits Week 96–Week 312, Unscheduled, and Early Withdrawal from Treatment (cont.)

Assessments	Clinic Visit (± 7 days) Weeks 96, 120, 144, 168, 192, 216, 240, 264, 288	Clinic Visit (± 3 days) Weeks 100, 104 , 112, 116, 124, 128, 136, 140, 148, 152, 160, 164, 172, 176, 184, 188, 196, 200, 208, 212, 220, 224, 232, 236, 244, 248, 256, 260, 268, 272, 280, 284, 292, 296, 304, 308	Clinic Visit (± 3 days) Weeks 108, 132, 156, 180, 204, 228, 252, 276, 300	Clinic Visit (–14 days) Week 312	Unscheduled Visit [c]	Early Withdrawal from Treatment Visit [d]
Pregnancy test [g]	x	*x*	x	x		x
Hematology	x		x	x	x [c]	x [m]
ESR [h]	x		x	x	x	x
Chemistry	x		x	x	x [c]	x [m]
Hepatitis B DNA [i]	x		x	x		
Serum sample (CRP)	x				x [c]	x [m]
Etrolizumab PK sample (serum) [j]	x		x	x	x	
Anti-drug antibody sample (serum) [j, k]	x		x	x	x [l]	x [l, m]
Etrolizumab administration	x	x	x	x		

Appendix 1c
Schedule of Assessments: Open-Label Extension Phase (cont.)

ADA = anti-drug antibody; BP = blood pressure; CRP = c-reactive protein; ECG = electrocardiogram; eCRF = electronic case report form; ESR = erythrocyte sedimentation rate; GI = gastrointestinal; PD = pharmacodynamics; PK = pharmacokinetic; PCDAI = Pediatric Crohn's Disease Activity Index; PML = progressive multifocal leukoencephalopathy; PUCAI = Pediatric Ulcerative Colitis Activity Index.

[a] Day 1 of Week 0.

[b] Week 0 procedures and laboratory assessments that have been collected as part of the final visit for the safety follow-up period (within the treatment phase) do not need to be repeated, with the exception of ADAs, which must be recollected at Week 1 if the Week 0 visit occurs > 7 days after the final visit of the safety follow-up period.

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

[d] Denotes the early withdrawal from treatment visit for the open-label treatment period. To be performed within 30 days of last dose of study drug. Study drug is not administered at the Early Withdrawal from Treatment visit.

[e] PML neurologic examination consists of the PML Subjective Checklist. Administer before other assessments, per Appendix 7.

[f] For children who are 6 years of age or younger, the parent or caregiver can respond to the questions on the patients behalf.

[g] A urine test may be performed; however, if the urine test result is positive, a confirmatory serum test must be performed. Do not administer etrolizumab unless the serum pregnancy test result is negative. A urine pregnancy test is only required in female patients at Tanner Stage 2 or greater, or after onset of menarche. Test must be performed on fresh voided sample.

[h] For patients with Crohn's disease only. Hematocrit, albumin, and erythrocyte sedimentation rate (ESR) will be collected to calculate the PCDAI score.

[i] Assessment is required if the patient becomes Hepatitis B antibody positive. Not mandatory for all patients.

[i] All samples to be collected prior to administration of etrolizumab.

[k] If serum sickness or a clinically significant allergic drug reaction is suspected, Sponsor should be notified, and serum for etrolizumab level and ADAs should be drawn and sent to the central laboratory. ADA samples may also be utilized for exploratory PD assessments or assessment of drug concentrations.

[l] PD and drug concentrations may be assessed from these ADA samples.

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

Appendix 1d
Schedule of Assessments: 12-week Safety Follow-Up After Completion or Early Termination of Open-Label Extension Phase

Assessments	*Week (±3 days)*			
	Week 4 [a]	*Week 8* [a]	*Week 12 or Early Withdrawal Visit* [b]	*Unscheduled Visit* [c]
Concomitant medications	*x*	*x*	*x*	*x*
Adverse events	*x*	*x*	*x*	*x*
Urine pregnancy test [d]			*x*	
Physical examination			*x*	
Anti-drug antibody sample (serum) [e]			*x*	
PML neurologic examination [f]			*x*	

ADA =anti-drug antibody; PD =pharmacodynamic; PK =pharmacokinetic; PML =progressive multifocal leukoencephalopathy.

[a] *Week 4 and Week 8 study assessments are to be made by telephone call and not by clinic visit.*

[b] *All assessments indicated for the Early Withdrawal Visit should be performed if the patient discontinues prior to completion of the 12-week safety follow-up period.*

[c] *Unscheduled visit for safety monitoring.*

[d] *A urine test may be performed; however, if urine test result is positive, a confirmatory serum test must be performed. A urine pregnancy test is only required in female patients at Tanner Stage 2 or greater, or after onset of menarche. The test must be performed on a fresh voided sample.*

[e] *If serum sickness or a clinically significant allergic drug reaction is suspected, the Sponsor should be notified, and serum for the analysis of study drug level and ADA should be drawn. If etrolizumab concentrations or PD assessments are needed then ADA sample can be used.*

[f] *PML neurologic examination consists of the PML Subjective Checklist. Administer before other assessments as per Appendix 7.*

Appendix 1e
Schedule of Assessments: Progressive Multifocal Leukoencephalopathy Monitoring Phase

	Extended PML Monitoring Phase [a]	
Assessments	24, 48, 68, and 92 [b] Weeks after Discontinuation from Study Treatment [c] OR Symptom-Driven Unscheduled Telephone Call [d] OR Early Termination [e, f,] OR After Completion of OLE [g]	Unscheduled Visit [h]
PML Subjective Checklist [i]	x	x
Adverse event reporting to the Sponsor [j]	x	x

OLE=open-label extension; PML=progressive multifocal leukoencephalopathy.

Note: The extended PML monitoring period is to be conducted for patients completing or discontinuing from the randomized treatment phase after completion of the safety follow-up AND for patients entering *or discontinuing* from the open-label extension phase.

[a] The total length of the PML monitoring period is 104 weeks. The extended PML monitoring period telephone calls will occur at the indicated timepoints for the extended PML monitoring period. The extended PML monitoring will be conducted using a PML Subjective Checklist over the telephone. PML monitoring should occur within 7 days of the specified day.

[b] *P*atients that complete the 24-week treatment phase but do not enter the OLE phase. The last PML monitoring call will be 92 weeks after completion of the randomized treatment phase. For patients that discontinue early from the treatment phase, the last PML monitoring call will be 96 weeks after discontinuation. For the patients that complete OLE, the last PML monitoring call will be 104 weeks after OLE completion.

[c] For patients that complete the treatment phase, the PML monitoring phase includes Week 12 to Week 16 of the treatment phase plus the 8-week safety follow-up and the 92-week PML safety monitoring phase.

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

[e] For patients that discontinue early from the 24-week randomized treatment phase, the PML monitoring phase includes 8-week safety follow up and 96 weeks of PML safety monitoring.

[f] For patients that discontinue after the 24-week randomized treatment phase but prior to study completion (end of extended PML monitoring period), the early termination visit from the extended PML monitoring period should be performed (a subjective checklist by telephone).

[g] For patients that complete the OLE *treatment,* the PML monitoring phase includes 104 weeks of PML safety monitoring.

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

[i] If there are any signs or symptoms suggestive of PML identified on the subjective checklist during the telephone call, the patient will be asked to come into the clinic for further evaluation and if indicated referral to a neurologist. .

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

Appendix 2
Pediatric Ulcerative Colitis Activity Index (PUCAI)

ITEM	POINTS
1. Abdominal pain:	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
2. Rectal bleeding	
None	0
Small amount only, in less than 50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
3. Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
4. Number of stools per 24 hours	
0-2	0
3-5	5
6-8	10
>8	15
5. Nocturnal bowel movement (any diarrhea episode causing wakening)	
No	0
Yes	10
6. Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
SUM OF PUCAI (0-85)	

Appendix 2
Pediatric Ulcerative Colitis Activity Index (PUCAI) (cont.)

PUCAI User Guide

Most items contained in the PUCAI can be scored using the instructions provided within the instrument. The following issues require additional clarification.

Time period for evaluation

- Answers should reflect a daily average of the last two days.
- However, if clinical conditions are changing rapidly (e.g., during intense intravenous therapy), the previous 24 hours should be considered.
- For patients undergoing colonoscopy, answers should reflect the two days before bowel cleanout was started.

Activity level

- Occasional limitation of activity= could attend school or equivalent, but reduced activity (e.g., attends school but does not play at breaks).
- Severe restricted activity=could not attend school or equivalent activity.

PUCAI definitions of disease activity, remission, and response to therapy

(all are based on analysis of data generated during development process during 2006)

- **Remission**: total score less than 10 points
- **Mild disease activity:** total score between 10 and 30 points inclusive
- **Moderate disease activity:** total score between 35 and 60 points inclusive
- **Severe disease activity:** total score of 65 points or greater
- **Response** (minimal clinically significant change in score over time): a change in score of at least 20 points.

Appendix 3
Pediatrics Crohn's Disease Activity Index (PCDAI)

ITEM	POINTS
Abdominal pain	
None	0
Mild (brief episodes, not interfering with activities)	5
Moderate/severe (frequent or persistent, affecting with activities)	10
Stools	
0-1 liquid stools, no blood	0
2-5 liquid or up to 2 semi-formed with small blood	5
Gross bleeding, >6 liquid stools or nocturnal diarrhoea	10
Patient functioning, general well-being (Recall, 1 week)	
No limitation of activities, well	0
Occasional difficulties in maintaining age appropriate activities, below par	5
Frequent limitation of activities, very poor	10
EXAMINATION	
Weight	
Weight gain or voluntary weight loss	0
Involuntary weight loss 1-9%	5
Weight loss >10%	10
Height	
< 1 channel decrease (or height velocity > -SD)	0
> 1<2 channel decrease (or height velocity < -1SD> -2SD)	5
> 2 channel decrease (or height velocity < -2SD)	10
Abdomen	
No tenderness, no mass	0
Tenderness, or mass without tenderness	5
Tenderness, involuntary guarding, definite mass	10
Peri-rectal disease	
None, asymptomatic tags	0
1-2 indolent fistula, scant drainage, tenderness of abscess	5
Active fistula, drainage, tenderness or abscess	10
Extra-intestinal manifestations	
Fever > 38.5 x 3 days in week, arthritis, uveitis, erythema nodosum, or pyoderma gangrenosum	
None	0
One	5
Two	10
LABORATORY	
Hct (%)	
<10yrs / 11-14 (male) / 11-19 (female) / 15-19 (male)	
> 33 / > 35 / > 34 / > 37	0
28-33 / 30-34 / 29-33 / 32-36	2.5
< 28 / < 30 / < 29 / < 32	5
ESR (mm/hr)	
< 20	0
20-50	2.5
> 50	5
Albumin (g/L)	
>35	0
31-34	5
<30	10

Disease activity
<10 – remission
10-27.5 – mild
30-37.5 – moderate
>40 – severe

TOTAL =

Appendix 4
Anaphylaxis Precautions

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug administration:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intravenous, intramuscular, and endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug administration:

- Stop the study drug infusion.
- Call for additional medical assistance.
- Maintain an adequate airway.
- Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
- Administer antihistamines, epinephrine, or other medications as required by patient status and as directed by the physician in charge.
- Continue to observe the patient and document observations.
- Draw serum/plasma samples for immunogenicity testing.
- Ask patient to return for washout immunogenicity sample if appropriate.

Appendix 5
Tanner Stages

Sexual Maturity Stages in Boys and Girls

	Male Genitalia	Pubic Hair	Female Breasts
1	Preadolescent—testes, scrotum, and penis are childlike in size	Stage None; may be vellus hair, as over abdomen	Preadolescent—elevation of papilla only
2	Slight enlargement of scrotum with reddening of skin; little or no enlargement of penis	Sparse growth of long, slightly pigmented, downy hair, straight or slightly curled, primarily at base of penis or along labia	Breast bud stage; breast and papilla form a small mound; areolar diameter enlarges
3	Further enlargement of scrotum; penis enlarges, mainly in length	Hair considerably darker, coarser, and more curled; spreads sparsely over junction of pubes	Further enlargement of breast and areola with no separation of their contours
4	Further enlargement and darkening of scrotum; penis enlarges, especially in breadth; glans develops	Adult-type hair that does not extend onto thighs, covering a smaller area than in adult	Areola and papilla project to form a secondary mound above the contour of the breast; stage 4 development of the areolar mound does not occur in 10% of girls and is slight in 20%; when present, it may persist well into adulthood
5	Adult in size and shape	Adult in quantity and type with extension onto thighs but not up linea alba	Mature female; papilla projects and areola recesses to general contour of breast

Data from Tanner JM: Normal growth and techniques of growth assessment. Clin Endocrinol Metab 15:436, 1986.

In boys, if different scores are obtained for pubic hair and genitalia, the score for genitalia should be used.

In girls, if different scores are obtained for pubic hair and breast development, the score for breast development should be used.

Appendix 6
Childbearing Potential, Pregnancy Testing, and Contraception

All females 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). See Section 5.4.3 of the protocol for management of a patient with a confirmed pregnancy.

All postpubertal female patients are considered to be of childbearing potential unless they meet one of the following criteria:

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

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

> Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Examples of highly effective contraception include the following:

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

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

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

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 7
Worksheet for the PML Neurologic Examination

PML Subjective Checklist of neurologic assessment to monitor for progressive multifocal leukoencephalopathy (PML) in the Etrolizumab Pediatric Studies

PML usually manifests with subacute, progressive neurologic deficits including:

Neurologic Domain	Signs/Symptoms	Relevant PML Subjective 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 systematic review of symptoms seeking any new neurological deficits will be performed with the patient and parents. Significant new symptoms should trigger referral to a pediatric neurology specialist to confirm and investigate.

At screening and all other visits the PML Subjective Checklist should be performed.

During the evaluation, if there is a “yes” response to the questions, the symptoms of the patient should be discussed with the patient or patients parent/legal guardian to confirm that these are new and significant changes that cannot be ruled out by every day events.

Appendix 7
Worksheet for the PML Neurologic Examination (cont.)

PML Subjective Checklist

Symptoms	"Compared to how you (your child) usually feel, have you (your child) had a significant change in any of the following?"		If the answer is "Yes", obtain a description of the symptom(s) with examples
	YES	NO	
1) Have you (your child) experienced any new difficulty with vision (ex. Blurred vision or seeing double), new difficulty with reading, or loss of vision?			
2) Have you (your child) had new onset difficulty speaking, understanding, or communicating. (e.g., word finding trouble, using the wrong words)			
3) Have you (your child) been experiencing new onset weakness in face, arms and/or legs?			
4)Has your child recently developed clumsiness, difficulty with balance, or falling more than normal?			
5. Has your child recently developed difficulty understanding others, or been less aware of the environment?			

Appendix 7
Worksheet for the PML Neurologic Examination (cont.)

6. Has your child experienced change in behavior, or new problems with attention, recall, memory, or thinking?			
7. Have you (your child) been experiencing any new numbness or other loss of sensation?			

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

- If there is a clinically significant abnormal finding on the PML Subjective Checklist, this should be appropriately documented on the worksheet and in the eCRF.
- If there are any clinically significant abnormalities found on the PML Subjective 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)

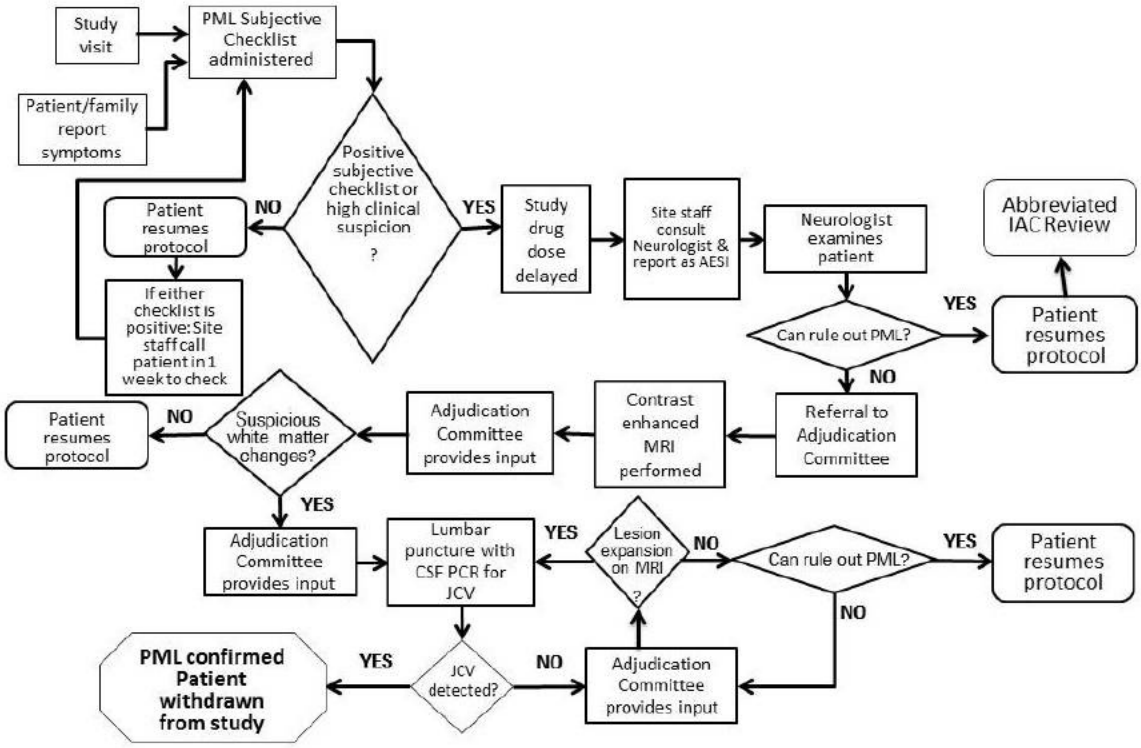
If yes, date of administration of PML Subjective Checklist (Date)

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

Is PML suspected? (Yes/No)

Appendix 8
Algorithm for Evaluation of Progressive Multifocal Leukoencephalopathy

- If there is a clinically significant positive finding on the PML Subjective Checklist, this should be appropriately documented.
- If there are any clinically significant abnormalities found on the PML Subjective 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 9
Clinical Criteria for Diagnosing Anaphylaxis

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

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

AND AT LEAST ONE OF THE FOLLOWING:

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

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

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

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

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

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

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