Official Title:	A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Etrolizumab as an Induction And Maintenance Treatment For Patients With Moderately to Severely Active Crohn's Disease
NCT Number:	NCT02394028
Document Date:	Protocol Version 7: 24-April-2019

PROTOCOL

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ETROLIZUMAB AS AN INDUCTION AND MAINTENANCE TREATMENT FOR PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE**
PROTOCOL NUMBER:	GA29144
VERSION NUMBER:	7
EUDRACT NUMBER:	2014-003824-36
IND NUMBER:	119725
TEST PRODUCT:	Etrolizumab (RO5490261)
MEDICAL MONITOR:	[redacted], M.D., M.S.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 6 October 2014
DATES AMENDED:	Version 2: 14 October 2014 Version 3: 9 December 2014 Version 4: 7 October 2015 Version 5: 19 November 2016 Version 6: 31 August 2017 Version 7: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	24-Apr-2019 20:35:41

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PROTOCOL AMENDMENT, VERSION 7: RATIONALE

Protocol GA29144 has been amended primarily to address a change in the Maintenance Phase sample size. Changes to the protocol, along with a rationale for each change, are summarized below:

- After reassessment of statistical assumptions, the projected sample size of patients enrolled into the Maintenance Phase has been reduced to approximately 480 patients. This sample size will still permit analysis of each of the co-primary maintenance endpoints at greater than 90% power and the key secondary maintenance endpoints at 80% power. The total number of patients randomized into the Induction Phase will not change (n =approximately 1150), and those patients will be followed through at least the end of the Induction Phase or early withdrawal from the Induction Phase (Sections 3.1.1, 3.1.3, 3.1.4, 6.1.2).
- Enrollment into the Maintenance Phase will stop after the sample size of approximately 480 patients has been achieved. Patients who are in the Induction Phase after closure of enrollment into the Maintenance Phase will continue to have the opportunity to enroll in Part 1 of the open-label extension–safety monitoring (OLE-SM) study (GA29145), if eligible, upon completion of the Induction Phase at Week 14 or in the event of disease worsening, as per protocol, between Weeks 10 and 14 (Section 4.5.9.1).
- The end of study has been amended to accommodate the closure of enrollment into the Maintenance Phase upon achievement of the required sample size (Section 3.2).

Additional changes that have been made to the protocol are as follows:

- [redacted]
- It has been clarified that medications equivalent to azathioprine and 6-mercaptopurine are permitted during this study (Sections 3.1.2, 4.1.1, 4.1.2, 4.4.2, 4.4.3, 4.4.5, and 5.1.1.1.1).
- Language regarding pharmacokinetic (PK) analyses has been clarified and modified to include analysis of the Week 10 PK sample (Sections 2.3, 3.4.4, and 6.6).
- Antagonists of IL-23±IL-12 (e.g., ustekinumab) have been added to the list of therapies prohibited during the study (Section 4.4.5).
- The statement requiring immediate reporting of any patient withdrawing from the study prior to Week 66 has been removed, as the decision to withdraw is at the discretion of the patient and investigator, and the patient continues to be monitored by the investigator after withdrawal (Section 4.5.5).

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ETROLIZUMAB AS AN INDUCTION AND MAINTENANCE TREATMENT FOR PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE**
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SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ETROLIZUMAB AS AN INDUCTION AND MAINTENANCE TREATMENT FOR PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE**
PROTOCOL NUMBER:	GA29144
VERSION NUMBER:	7
EUDRACT NUMBER:	2014-003824-36
IND NUMBER:	119725
TEST PRODUCT:	Etrolizumab (PRO145223)
PHASE:	Phase III
INDICATION:	Crohn's Disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Co-Primary Efficacy Objectives

The co-primary efficacy endpoints for this study are the following:

- Clinical remission, defined as a liquid/soft stool frequency (SF) mean daily score ≤ 3 and an abdominal pain (AP) mean daily score ≤ 1 with no worsening in either subscore compared to baseline, averaged over the 7 days prior to visit
- Endoscopic improvement, defined as a $\geq 50\%$ reduction from the baseline Simple Endoscopic Score for Crohn's Disease (SES-CD)

Primary efficacy objectives for this study will be analyzed separately for the Induction and Maintenance Phases as outlined below.

Induction Phase: To independently evaluate the efficacy of etrolizumab dose regimens compared with placebo in inducing clinical remission and endoscopic improvement at the end of the Induction Phase (Week 14)

Maintenance Phase: To independently evaluate the efficacy of etrolizumab compared with placebo in achieving clinical remission and endoscopic improvement at 1 year of maintenance treatment (Week 66), for patients who achieved a Crohn's Disease Activity Index (CDAI)–70 response (defined as a decrease of at least 70 points from baseline CDAI) at Week 14

Secondary Efficacy Objectives

Induction Phase

- To evaluate the efficacy of etrolizumab compared with placebo in achieving clinical remission at Week 6
- To evaluate the efficacy of etrolizumab compared with placebo in achieving an SES-CD ≤4 (≤2 for ileal patients), with no segment having a subcategory score (i.e., for ulceration size and extent, affected surface, or narrowing) that is >1, at Week 14

- To evaluate the reduction in CD signs and symptoms achieved by etrolizumab dose regimens compared with placebo at Week 14 as assessed by the Crohn's Disease Patient-Reported Outcome Signs and Symptoms (CD-PRO/SS) measure

Maintenance Phase

All secondary Maintenance endpoints are for patients who achieved CDAI-70 at Week 14, unless otherwise stated.

- To evaluate the efficacy of etrolizumab compared with placebo in maintaining clinical remission at Week 66 for patients who achieved clinical remission at Week 14
- To evaluate the efficacy of etrolizumab compared with placebo in achieving corticosteroid-free clinical remission at Week 66 *among patients who were receiving corticosteroids at baseline*
- To evaluate the efficacy of etrolizumab compared with placebo in maintaining endoscopic improvement at Week 66 for patients who achieved endoscopic improvement at Week 14
- To evaluate the efficacy of etrolizumab compared with placebo in achieving a SES–CD ≤4 (≤2 for ileal patients), with no segment having a subcategory score (i.e., for ulceration size and extent, affected surface, or narrowing) that is >1, at Week 66
- To evaluate the efficacy of etrolizumab compared with placebo in achieving durable clinical remission during 1 year of maintenance therapy (i.e., at ≥4 of the 6 in-clinic assessment visits that are conducted during the Maintenance Phase at Weeks 24, 28, 32, 44, 56, and 66)
- To evaluate corticosteroid-free clinical remission at Week 66 (off corticosteroid for at least 24 weeks prior to Week 66) in patients who were receiving corticosteroids at baseline
- To evaluate change in CD signs and symptoms from baseline to Week 66 as assessed by the CD-PRO/SS measure

[redacted]

Safety Objectives

The safety objectives for this study are:

- To evaluate the overall safety and tolerability of etrolizumab compared with placebo during Induction and Maintenance Phases of therapy
- To evaluate the incidence and severity of infection-related adverse events
- To evaluate the incidence of malignancies
- To evaluate the incidence and severity of immunogenic responses (anti-therapeutic antibodies [ATAs])
- To evaluate the incidence and severity of hypersensitivity reaction events

Pharmacokinetic Objectives

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

- To evaluate etrolizumab serum concentrations *during* the Induction Phase (Week 14) and at several predose timepoints when at steady state during the Maintenance Phase in patients who are re-randomized to etrolizumab
- To characterize the interindividual variability and potential covariate effects on etrolizumab serum exposure
- To investigate the relationship between serum exposure and clinical response and remission as well as endoscopic changes during the induction and maintenance treatment phases
- To characterize the PK profile of etrolizumab in patients with CD and the relationship between serum exposure of etrolizumab and $\beta 7$ receptor occupancy by etrolizumab on peripheral blood T and B lymphocytes subsets (in a PK/PD substudy)

[redacted]

Study Design

Description of Study

This is a multicenter, Phase III, double-blind, placebo-controlled study evaluating the efficacy, safety, and tolerability of etrolizumab compared with placebo during induction and maintenance treatment of moderate to severely active CD. Patients enrolled in this study may be eligible to participate in an open-label extension–safety monitoring (OLE-SM) study (GA29145), which consists of two parts: Part 1 (designated OLE [open-label extension]) and Part 2 (designated SM [safety monitoring]).

The study design will consist of 1) a Screening Phase (up to 35 days) to determine patients' eligibility for the study, 2) an Induction Phase (14 weeks), followed by 3) a Maintenance Phase (52 weeks) in patients demonstrating a CDAI-70 response at the end of the Induction Phase, and 4) a Safety Follow-Up Phase (12 weeks) after administration of the last dose of study drug in the Maintenance Phase for those patients who do not participate in Part 1 (OLE) of Study GA29145. At the completion of the Safety Follow-Up Phase, patients will be asked to

enter an extended PML-monitoring phase Part 2 (SM) of Study GA29145 for 92 weeks. An independent Data Monitoring Committee (iDMC) will monitor safety and study conduct on an ongoing basis.

Patients in all cohorts will be required to provide blood samples for population PK analysis and PD characterization. Patients will also have an option to consent and participate in a PK/PD substudy. The objective of the substudy is to determine the relationship between etrolizumab exposure and receptor occupancy in peripheral blood in patients with CD. To achieve this objective, it is planned that approximately 150 *evaluable* patients will be enrolled in the substudy. Blood sampling for the PK/PD substudy will continue in the Maintenance Phase.

Moderate to severely active CD will be defined at baseline by clinical signs and symptoms that result in a CDAI score between ≥ 220 and ≤ 480, as well as either an average SF ≥6 or an average SF >3 and average AP >1, calculated on the day of randomization using electronic diary (e-diary) PRO data from the 7 days prior to randomization. In conjunction, the presence of active inflammation, defined as a SES-CD of ≥ 7, or ≥ 4 in cases of isolated ileitis or post-ileocecal resection, is required and will be determined by a screening ileocolonoscopy scored using the central read model.

The study population will consist of patients who are refractory or intolerant to one or more of the following therapies: 1) corticosteroid (CS), 2) immunosuppressant (IS), or 3) anti- tumor necrosis factor (TNF) (or inadequate response to anti-tumor necrosis factor [TNF-IR]). Patients who enroll on the basis of refractory or intolerance to CS and/or IS may have been previously exposed to ant-TNFs or be naïve to anti-TNFs.

Approximately 1150 patients will be randomized into the study from approximately 420 global investigational sites via enrollment into one of three cohorts. The enrollment will be sequential, first into Cohort 1, then Cohort 2, and lastly Cohort 3.

Overview of Screening Phase

Patients will be evaluated for eligibility in the 35-day Screening Phase. Assessments for eligibility are noted in the protocol.

During the Screening Phase, patients taking CS therapy must have been on a stable dose of ≤ 20 mg/day prednisone or equivalent or ≤ 6 mg/day oral budesonide for at least 2 weeks immediately prior to their randomization. Similarly, eligible patients requiring background IS therapy (e.g., azathioprine [AZA] *[or equivalent]*, 6-mercaptopurine [6-MP] *[or equivalent]*, or methotrexate [MTX]) must be receiving a stable IS dose regimen for at least 8 weeks immediately prior to their randomization. Patients who have been treated with anti-TNF therapy must have discontinued this treatment for at least 8 weeks prior to their randomization.

The ileocolonoscopy should be performed during the Screening Phase and at least 9 days prior to randomization to allow sufficient time for a central reader scoring and determination of eligibility, and to avoid the ileocolonoscopy bowel preparation influencing the patient reported outcomes used in the determination of baseline SF, AP, and CDAI scores (i.e., abdominal pain, general well-being, and stool frequency)

Overview of Induction Phase

Eligible patients will be enrolled sequentially into one of three cohorts for the 14-week Induction Phase.

Patients enrolled in Cohort 1 (double-blind, placebo-controlled, exploratory cohort; $n = 300$) will be randomized in a 1:2:2 ratio to receive placebo, etrolizumab 105 mg subcutaneously (SC) every 4 weeks (Q4W) (low dose), or etrolizumab 210 mg SC (high dose) at Weeks 0, 2, 4, 8, and 12 within a 14-week Induction Phase (note that patients randomized to low-dose etrolizumab and patients randomized to placebo will receive one placebo injection at Week 2, see below). Patients enrolled in Cohort 2 (etrolizumab dose–blind, active-treatment cohort; $n = 350$) will be randomized in a 1:1 ratio to receive low-dose or high-dose regimens of etrolizumab. Patients enrolled in Cohort 3 (double-blind, placebo-controlled, pivotal cohort; $n = 500$) will be randomized in a 2:3:3 ratio to receive placebo or etrolizumab low-dose or high-dose. Because the low dose and high dose of etrolizumab are in syringes of different volumes, in order to preserve the blind, patients in all three cohorts will receive two injections at Weeks 0, 4, 8, and 12. Patients randomized to low-dose etrolizumab will receive one placebo (matching high-dose prefilled syringe) and one low-dose etrolizumab injection at each administration except at Week 2, when they will receive one placebo injection. Patients randomized to

high-dose etrolizumab will receive one placebo and one high-dose etrolizumab injection at each administration, except at Week 2 where they will receive one high-dose injection. Finally, patients randomized to placebo will receive two placebo injections at every administration, except at Week 2 where they will receive one placebo injection.

The randomization in all cohorts will be stratified by concomitant oral CS treatment (yes vs. no), concomitant IS treatment (yes vs. no), baseline CDAI ≤330 (yes vs. no), and prior anti-TNF exposure (yes vs. no). The enrollment will be managed to ensure that the proportion of the TNF-exposed patients in Cohort 3 does not exceed approximately 60% and that the proportion of patients with a CDAI score between >450 and ≤480 does not exceed approximately 10% in each cohort.

During the Induction Phase, patients in all cohorts should keep their dose(s) of CS and IS therapy stable (if requiring CS/IS at baseline). Increase in dose of these medications will be considered rescue therapy. Also, every attempt should be made to keep anti-diarrheal medication at a fixed dose, if required. The impact of titrating anti-diarrheal medication on the placebo response rate for SF and AP has not been studied in a moderate to severely active CD population; dose adjustments may confound the data interpretation. Changes to any concomitant medications must be documented in the electronic Case Report Form (eCRF).

Between and including Weeks 10 and 14, there is an optional escape to Part 1 (OLE) of Study GA29145, where patients can receive open-label etrolizumab. This can only be exercised if a patient experiences disease worsening, defined as a CDAI Week 10 score greater than the patient's baseline (Week 0) score.

At Week 14, patients achieving CDAI-70 response without the use of rescue therapy will continue to the Maintenance Phase *until a sample size of approximately 480 patients enrolled in the Maintenance Phase has been achieved*. Patients not eligible for the Maintenance Phase may be eligible for Part 1 (OLE) of Study GA29145.

Patients who are in the Induction Phase after closure of enrollment into the Maintenance Phase may enroll in Part 1 (OLE) of Study GA29145, if eligible, upon completion of the Induction Phase at Week 14 or in the event of disease worsening, as specified above, between Weeks 10 and 14

Patients who require surgical intervention for CD at any time during the Induction Phase will stop study treatment, enter the Safety Follow-Up Phase, and will be asked to enter Part 2 (SM) of Study GA29145 for PML monitoring. Patients who self-withdraw from the Induction Phase and do not meet the eligibility criteria for OLE treatment will also enter the Safety Follow-Up Phase and be asked to enter Part 2 (SM) of Study GA29145 for PML monitoring.

Concomitant CD Therapy in the Induction Phase

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening to the study completion/early termination visit.

Anti-diarrheal medications are permitted if used to manage chronic diarrhea but every attempt should be made to keep the dose/regimen stable. Any changes in the dose/regimen after baseline (Week 0) must be captured by the investigator and/or patient.

Occasional use of nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen is permitted for pain relief (e.g., in the case of headache, arthritis, myalgia, etc.). Prophylactic aspirin use up to 325 mg/day is also permitted.

Patients should not be treated for continuing signs and symptoms of CD with any medication that is prohibited to be taken concomitantly with etrolizumab; these include but are not limited to: anti-integrins, anti-adhesion molecules (e.g., anti-MAdCAM-1), T- or B- cell-depleting agents with the exception of AZA and 6-MP *(or equivalent)*, TNF antagonists, *antagonists of IL-23 ±IL-12 (e.g., ustekinumab),* anti-metabolites, cyclosporine, and tacrolimus.

CS enemas/suppositories and/or topical (rectal) 5-aminosalicylate (5-ASA) preparations are also prohibited medications. Patients taking these medications will be considered non-responders for the purpose of any endoscopic analyses. These treatments must be discontinued, but patients may continue to receive etrolizumab and may still be eligible for Part 1 (OLE) of Study GA29145.

Rescue Therapy in the Induction Phase

This is defined as medication prescribed for new or worsening CD symptoms, and includes:

- Any new CS or IS therapy for CD
- Any increase in dose or regimen of baseline Crohn's medications

Antibiotics, 5-ASAs, anti-diarrheals, probiotics, herbal/ayurvedic, nutritional and homeopathic supplements are not considered as rescue therapies.

Patients requiring rescue medication during the Induction Phase will be considered non-responders for the primary analysis and will not be eligible for the Maintenance Phase.

Overview of Maintenance Phase

At the end of the Induction Phase (Week 14), patients will be assessed for a CDAI score and will undergo a full endoscopy (ileocolonoscopy) with central reading to determine an SES-CD. Every attempt must be made to schedule the ileocolonoscopy to take place at the Week 14 visit or no later than 5 calendar days after this visit; the procedure must not be scheduled before Week 14. The patient-reported outcomes e-diary data (i.e., abdominal pain, general well-being, and stool frequency) that are captured in the 7 days prior to the bowel preparation will be used to calculate the Week 14 SF, AP, and CDAI scores, thus removing any influence of the bowel preparation on these outcomes.

Patients who received placebo during the Induction Phase and achieved a CDAI-70 response will undergo a sham randomization to blinded placebo maintenance treatment. Patients who received etrolizumab and achieved a CDAI-70 response at Week 14 without the use of rescue therapy will be randomized into the Maintenance Phase in a 1:1 ratio to treatment with placebo or etrolizumab 105 mg SC Q4W. *This will continue until a sample size of approximately 480 patients enrolled in the Maintenance Phase has been achieved.*

The randomization call may take place between Week 14 (last visit in the Induction Phase) and Week 16, provided the patient has been assessed as eligible for the Maintenance Phase. The randomization will be stratified by CDAI remission at both Weeks 10 and 14 (yes vs. no), induction dose regimen (low dose vs. high dose), concomitant oral CS treatment (yes vs. no), and prior anti-TNF exposure (yes vs. no). The first dose in the Maintenance Phase is administered at the Week 16 clinic visit.

Patients should remain on a stable dose of IS therapy throughout the treatment period, unless dose reduction or discontinuation is required because of a toxicity related to the medication. CS dose should be tapered starting at Week 14. Patients who cannot tolerate the CS taper without recurrence of CD symptoms or symptoms of steroid withdrawal can receive an increase in CS dose, but this should not exceed the dose administered at randomization. The dose-tapering regimen must be re-initiated within 2 weeks.

During the Maintenance Phase, patients who experience a clinical relapse may have the option of escaping to Part 1 (OLE) of Study GA29145. Clinical relapse is defined as meeting at least one of the following criteria on two consecutive visits (may include unscheduled visits), with at least one of the two consecutive CDAI scores ≥220:

- CDAI score ≥ the baseline (Week 0) score
- CDAI score ≥100 points higher than the Week 14 score

All patients who complete their final Maintenance Phase visit at Week 66 may be eligible to enroll in Part 1 (OLE) of Study GA29145. Patients who do not enroll in Part 1 (OLE) will enter a 12-week Safety Follow-Up Phase, after which they will be asked to enroll in a 92-week extended PML-monitoring phase (Part 2 [SM] of Study GA29145). Patients who require surgical intervention for CD at any time during the Maintenance Phase will stop study treatment, enter the Safety Follow-Up Phase, and will be asked to enter Part 2 (SM) of Study GA29145 for PML monitoring. Patients who self-withdraw from the Maintenance Phase and do not meet the eligibility criteria for OLE treatment will also enter the Safety Follow-Up Phase and be asked to enter Part 2 (SM) of Study GA29145 for PML monitoring.

Patients who withdraw will complete the early withdrawal assessments listed in the Schedule of Assessments; withdrawn patients will not be replaced.

Management of Concomitant CD Therapy in the Maintenance Phase

During the Maintenance Phase, corticosteroid dose should be tapered starting at Week 14 according to the following schedule:

- ≤ 20 mg/day prednisone (or equivalent): titrated via dose reduction of 2.5 mg/week until discontinuation
- ≤ 6 mg/day oral budesonide: titrated via dose reduction of 3 mg every 2-weeks until discontinuation

If needed, patients may increase their corticosteroid dose up to their baseline dose (i.e., dose at randomization), but the dose-tapering regimen should be re-initiated within 2 weeks.

Patients who are taking concomitant IS therapy (AZA, 6-MP, MTX) must remain on stable doses throughout the study unless dose reduction or discontinuation is required because of a toxicity related to the medication.

Doses of anti-diarrheal medication should also be kept stable.

Generally accepted criteria for discontinuation of IS due to toxicity include, but are not limited to, acute pancreatitis, severe leukopenia, severe thrombocytopenia, or significant elevations of the liver-associated enzymes from baseline, especially in the presence of an elevated total bilirubin. The ultimate decision to discontinue IS remains at the discretion of the Investigator.

Rescue Therapy in the Maintenance Phase

This is defined as medication prescribed for new or worsening CD symptoms, and includes:

- Any new CS or IS therapy for CD
- Increase in dose of IS therapy above the baseline (Week 0) dose
- Increase in the dose of CS therapy above a patient's baseline (Week 0) dose (applicable to patients requiring CS at baseline)

Antibiotics, 5-ASAs, anti-diarrheals, probiotics, herbal/ayurvedic, nutritional, and homeopathic supplements are not considered as rescue therapies.

Patients who require rescue therapy during the Maintenance Phase may be offered early access to the OLE (Study GA29145, Part 1), if eligible, and will be required to complete the Early Withdrawal visit assessment.

Prohibited therapies are as described for the Induction Phase.

Study Drug Administration

Patients will receive etrolizumab or placebo by SC injection according to their treatment assignment, as described below in "Investigational Medicinal Products". Patients and study personnel will be blinded to study drug assignment (or the etrolizumab dose assignment for Cohort 2 patients in the Induction Phase) for the entire study.

In the Induction Phase, study medication will be administered at the investigational site and patients will be trained to self-administer. A health care professional (HCP) will administer the first two doses, with the patient or their caregiver administering subsequent doses under HCP supervision. In the Maintenance Phase after completing Week 16, patients have the option to return to the investigational site or to self-administer/have a caregiver administer their dose Q4W at home within ±3 days of their scheduled dose unless a PK blood draw is planned, in which case the dose must be administered after the blood draw on the day of visit or within 3 days after the visit.

Schedule of Assessments

A schedule of study assessments is provided in Appendix 1 and a schedule of PK and PD assessments is provided in Appendix 1 and 3.

Number of Patients

Approximately 1150 patients will be randomized into the Induction Phase of the trial via enrollment into one of three cohorts.

Patients receiving etrolizumab in the Induction Phase who achieve a CDAI-70 response at Week 14 without the use of rescue therapy will be randomized into the Maintenance Phase of

the trial *until a sample size of approximately 480 patients enrolled in the Maintenance Phase is achieved. Of the approximately 480 patients enrolled in the Maintenance Phase, approximately 420 patients are estimated to be CDAI-70 responders who received etrolizumab during the Induction Phase and will be re-randomized to either etrolizumab 105 mg SC Q4W or placebo in the Maintenance Phase. The remaining approximately 60 patients are CDAI-70 responders who received placebo during the Induction Phase and will undergo a sham randomization to blinded placebo treatment during the Maintenance Phase.*

Target Population

The target population are refractory or intolerant to CS and/or IS therapy and who have either not received prior anti-TNF therapy (TNF-naive) or who have had prior exposure to one or more anti-TNF therapies, and who have had an inadequate response, refractory response, or intolerance to CS and/or IS therapy and/or anti-TNFs.

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Able and willing to provide written informed consent
- 18-80 years of age at time of consent
- For women who are not postmenopausal (at least 12 months of non–therapy-induced amenorrhea) or surgically sterile (e.g., absence of ovaries and/or uterus): agreement to remain abstinent or use a highly effective method of contraception (e.g., combined oral contraceptive pill or transdermal patch, spermicide and barrier [condoms], intrauterine device, implants for contraception, injections for contraception [with prolonged release], hormonal vaginal device, sterilization, or surgical tubal ligation for the duration of the study [i.e., during the treatment period and for at least 24 weeks after the last dose of study drug])

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent or use a condom, as well as not donate sperm during the treatment period and for at least 24 weeks after the last dose of study drug

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods for the partner) and withdrawal are not acceptable methods of contraception.
- Diagnosis of CD based on clinical, histopathological, and endoscopic evidence established ≥3 months prior to screening visit

  The Medical Monitor should be consulted in cases where CD was established at least 6 months prior to screening and a histopathology report is not available. The eligibility of the patient will be considered based on the weight of evidence supporting diagnosis and excluding other potential diagnoses.
- Moderately to severely active disease defined in the Screening Phase by:

  Clinical signs and symptoms resulting in a CDAI score of ≥220 to ≤480 calculated on the day of randomization, requiring a minimum of 4 days of e-diary PRO data from the 7 days prior to randomization **AND**

  A mean daily SF score ≥ 6 **OR** a mean daily SF > 3 and a mean daily AP score > 1 calculated on the day of randomization, requiring a minimum of 4 days of e-diary PRO data from the 7 days prior to randomization (applicable to Cohort 3, the pivotal cohort, only) **AND**

  The presence of active inflammation on screening ileocolonoscopy defined as a SES-CD of ≥7 or ≥4 in cases of isolated ileitis or post-ileocecal resection as determined by the central read model
- Involvement of ileum and/or colon with at least four colonic segments traversable by a pediatric endoscope or three segments (colon and/or ileum) for patients who have undergone a bowel resection for CD

- Meets the following surveillance colonoscopy requirements:

  Surveillance was undertaken at screening or ≤ 12 months prior in patients with colonic disease for > 10 years (regardless of any risk factors for bowel cancer).

  Surveillance was undertaken at screening or ≤ 5 years prior in patients with colonic disease for ≤ 10 years who have risk factors for bowel cancer.

  (Note—local colonic surveillance guidelines can be followed if patients have no risk factors and colonic disease for ≤ 10 years.)
- Have experienced intolerance, refractory disease, or no response (as defined below) to at least one of the following therapies within 5 years from screening:

CS Therapy

Refractory:

Has signs/symptoms of persistently active disease despite a history of at least one 4-week induction regimen including a dose equivalent to ≥ 30 mg/day prednisone for 2 weeks if oral or 1 week if IV or ≥ 9 mg/day oral budesonide

Intolerance to CS therapy:

History including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, and infection

IS Therapy

Refractory:

Has signs/symptoms of persistently active disease despite a history of at least one 12-week regimen of oral AZA *(or equivalent)* (≥ 1.5 mg/kg) or 6-MP *(or equivalent)* (≥ 0.75 mg/kg) or MTX (≥ 15 mg/week)

Intolerance to 6-MP *(or equivalent)*, AZA *(or equivalent)*, or MTX:

History of intolerance to AZA *(or equivalent)*, 6-MP *(or equivalent)*, and/or MTX (including, but not limited to, infection, nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopenia, and thiopurine methyltransferase genetic polymorphism)

Anti-TNF Therapy:

Inadequate primary non-response:

Did not respond (as evidenced by persistent signs/symptoms related to CD after receiving ≥ 2 induction doses of either infliximab [≥ 5 mg/kg] or adalimumab [160 mg/80 mg or 80 mg/40 mg] or certolizumab pegol [≥ 400 mg])

Inadequate secondary non-response:

Initially responded to induction therapy with infliximab (≥ 5 mg/kg) or adalimumab (≥ 40 mg) or certolizumab pegol (≥ 400 mg), but experienced signs/symptoms related to recurrence of CD during maintenance

Intolerance:

Experienced a significant injection-site reaction, congestive heart failure, infection, or other condition that precluded continuing use of anti-TNF therapy at any time

Patients who have not previously demonstrated inadequate response or intolerance to one or more anti-TNF therapies are eligible to participate in the study provided they are intolerant or refractory to corticosteroid or immunosuppressant therapy.

Exclusion Criteria

Exclusion Criteria Related to Gastrointestinal Health

- Has undergone subtotal colectomy with ileorectal anastomosis or has undergone total colectomy
- Short-bowel syndrome
- Has an ileostomy or colostomy

- Has evidence of fixed stenosis or small-bowel stenosis with prestenotic dilation that precludes adequate endoscopic assessment of the bowel
- Diagnosis of UC or indeterminate colitis
- Suspicion of ischaemic colitis, radiation colitis, or microscopic colitis
- Evidence of abdominal or perianal abscess
- Sinus tract with evidence for infection (e.g., purulent discharge) in the clinical judgment of the investigator. Fistulas related to Crohn's disease are not exclusionary.
- Expected to require surgery to manage CD-related complications during the study
- A history or evidence of adenomatous colonic polyps that have not been removed
- Past or present disease-related colonic mucosal dysplasia

Exclusion Criteria Related to Prior or Concomitant Therapy

- Any of the following treatments for CD within ≤ 8 weeks prior to randomization:
  - Adalimumab
  - Certolizumab pegol
  - Infliximab
- Any prior treatment with ustekinumab within 14 weeks prior to randomization
- Any prior treatment with etrolizumab or other anti-integrin agents (including vedolizumab, natalizumab, and efalizumab)
- Any prior treatment with anti-adhesion molecules (e.g., anti-MAdCAM-1)
- Prior treatment with T cell– or B cell–depleting agents (e.g., rituximab, alemtuzumab, or visilizumab) within ≤ 12 months prior to randomization, with the exception of AZA and 6-MP *(or equivalent)*.
- Any investigational treatment that included investigational vaccines within 12 weeks prior to randomization in the study or five 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)
- Treatment with corticosteroid enemas/suppositories and/or topical (rectal) 5-aminiosalicylate (5-ASA) preparations ≤ 2 weeks prior to randomization
- Continued tube feeding, defined formula diets, and/or parenteral alimentation/nutrition as treatment for CD ≥ 3 weeks prior to randomization
- Expectation of tube feeding, defined formula diets, and/or parenteral alimentation/nutrition as treatment for CD during the study
- Any live or attenuated vaccines ≤ 4 weeks prior to randomization
- Use of IV steroids during screening, with the exception of a single IV steroid dose administered in the Emergency Department
- Use of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil ≤ 4 weeks prior to randomization
- Chronic use of NSAIDs. Prophylactic aspirin use up to 325 mg/day is permitted, as is occasional use of NSAIDs for conditions such as headache, arthritis, myalgia, and menstrual cramps.
- If receiving oral CSs, patients will be excluded unless the dose is stable at ≤ 20mg/day prednisone or equivalent for ≥ 2 weeks immediately prior to randomization.
- If receiving ongoing treatment with oral 5-ASA, patients will be excluded if the dose is not stable for ≥ 2 weeks immediately prior to randomization.

- If receiving ongoing treatment with probiotics (e.g., Culturelle, Saccharomyces boulardii) or over-the-counter supplements (e.g., N-acetyl glucosamine, curcumin), patients will be excluded if the dose is not stable for ≥ 2 weeks immediately prior to randomization.
- If receiving ongoing treatment with ISs (e.g., 6-MP, AZA, or MTX), patients will be excluded if the dose is not stable for ≥ 8 weeks immediately prior to randomization.
- If receiving ongoing treatment with antibiotics for the treatment of CD, patients will be excluded if the dose is not stable for ≥ 2 weeks immediately prior to randomization.

Patients may continue to receive ongoing treatment with anti-diarrheals (e.g., loperamide or diphenoxylate with atropine), preferably achieving a stable dose for ≥ 2 weeks prior to randomization. However, if the patient and/or the treating physician decides to change the dose or course of anti-diarrheals at any time during screening, these patients will be allowed to participate in study.

Exclusion Criteria Related to Infection Risk

- Congenital or acquired immune deficiency
- Patients must undergo screening for HIV and test negative 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 antiviral treatment and an undetectable HCV RNA at screening or (2) has a known history of HCV antibody positivity with history of undetectable HCV RNA and undetectable HCV RNA at screening in the absence of history of HCV anti-viral treatment
- In the screening hepatitis B assessment (which consists of testing for hepatitis B surface antigen [HBsAg], hepatitis B core anti-body [HBcAb], and if required, hepatitis B virus [HBV] DNA), patients who test positive for HBsAg are excluded from the study. Patients who test positive for HBcAb but negative for HBsAg must have a confirmed negative HBV DNA test result to be eligible for the study and will be required to 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 infection with and/or treatment for *Clostridium difficile* or other intestinal pathogen treatment within 8 weeks prior to randomization.
- A history of active or latent tuberculosis (TB) confirmed by one of the following screening tests:

  Positive tuberculin (purified protein derivative-PPD) skin test

  Or

  Positive QuantiFERON®TB Gold test

  Patients with a documented history of BCG vaccination must have a negative QuantiFERON test result and negative chest radiograph (see below) to be eligible.
- 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 or disseminated viral infections
- Any serious opportunistic infections that occurred ≤ 6 months prior to screening
- Any current or recent signs or symptoms (≤ 8 weeks before screening) of infection, except for the following:

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

  Fungal infections of the nail beds

  Oral or vaginal candidiasis that has resolved with or without treatment prior to randomization

- Any major episode of infection requiring treatment with IV antibiotics ≤ 8 weeks prior to screening or oral antibiotics ≤ 4 weeks prior to screening. Treatment with antibiotics as adjunctive therapy for CD in the absence of documented infection is not exclusionary.

Exclusion Criteria Related to General Safety

- Pregnancy or lactation
- Lack of peripheral venous access
- Hospitalization (other than for elective reasons) within 4 weeks prior to randomization
- Inability to comply with study protocol, in the opinion of the investigator
- Significant uncontrolled comorbidity such as neurological, cardiac (e.g., moderate to severe heart failure New York Heart Association Class III/IV), pulmonary, renal, hepatic, endocrine, or GI disorders (other than CD)
- Neurological conditions or diseases that may interfere with monitoring for PML
- Clinically significant abnormalities on screening neurologic examination
- History of demyelinating disease
- History of major neurological disorders, including stroke, MS, brain tumor, neurodegenerative disease, or poorly controlled epilepsy
- History of alcohol, drug, or chemical abuse ≤ 6 months prior to screening
- Conditions other than CD that could require treatment with > 20 mg/day of prednisone (or equivalent) during the course of the study
- History of cancer, including hematologic malignancy, solid tumors, and carcinoma in situ within 5 years before screening

  Non-serious basal cell 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 cervical smear result at any time that indicated the presence of adenocarcinoma in situ (AIS), high-grade squamous intraepithelial lesions (HSIL), or cervical intraepithelial neoplasia (CIN) of Grade > 1
- History of organ transplant or cell transplantation
- Presence of metal in the body that could a pose hazard during any potential scanning in patients for whom a magnetic resonance imaging (MRI) scan is considered unsafe

Exclusion Criteria Related to Laboratory Values (at Screening)

- Serum creatinine > 2 times the upper limit of normal (ULN)
- Impaired hepatic function defined by one of the following:

  Serum transaminases $> 3 \times$ ULN

  Alkaline phosphatase $> 3 \times$ ULN

  Total bilirubin $> 2.5 \times$ ULN (excluding inherited deficiencies such as Gilbert's disease)
- Platelet count $< 100{,}000/\mu L$
- Hemoglobin < 8 g/dL
- Absolute neutrophil count $< 1500/\mu L$
- Absolute lymphocyte count $< 500/\mu L$

Length of Study

The study duration, from screening to end of study participation for a given eligible patient, will be up to 82 weeks (4-week screening period + 14-week Induction Phase + 52-week Maintenance

Phase + 12-week Safety Follow-up Phase). The total length of the treatment period will be 66 weeks (14-weeks Induction Phase + 52-week Maintenance Phase).

Those who do not enroll in Part 1 (OLE) of Study GA29145 will continue to 12 weeks of safety follow-up in this study and then be asked to enroll in Part 2 (SM) of Study GA29145 for 92 weeks of monitoring for PML.

End of Study

The end of the study is defined as *meeting one of the following criteria, whichever is later:*

- *Completion of the 12-week Safety Follow-up Phase for the last patient in the Induction Phase*
- The final visit for the last *Induction* patient transferred to Part 1 (OLE) of Study GA29145
- *Completion of the 12-week Safety Follow-up Phase for the last patient in the Maintenance Phase*
- *The final visit for the last Maintenance patient transferred to Part 1 (OLE) of Study GA29145*

Outcome Measures

Co-Primary Efficacy Outcome Measures

Induction Phase

- Clinical remission at Week 14
- Endoscopic improvement at Week 14

Maintenance Phase*, among patients who achieve CDAI-70 response at Week 14*

- Clinical remission at Week 66
- Endoscopic improvement at Week 66

Secondary Efficacy Outcome Measures

Induction Phase

- Clinical remission at Week 6
- SES–CD ≤4 (≤2 for ileal patients), with no segment having a subcategory score (i.e., for ulceration size and extent, affected surface, or narrowing) that is >1, at Week 14
- Change in CD signs and symptoms from baseline to Week 14 as assessed by the CD-PRO/SS measure

Maintenance Phase

- Clinical remission at Week 66 among patients who achieved clinical remission at Week 14
- Corticosteroid-free clinical remission at Week 66 *among patients who were receiving corticosteroids at baseline*
- Endoscopic improvement at Week 66 among patients who achieved endoscopic improvement at Week 14
- SES–CD ≤4 (≤2 for ileal patients), with no segment having a subcategory score (i.e., for ulceration size and extent, affected surface, or narrowing) that is >1, at Week 66
- Durable clinical remission
- Corticosteroid-free clinical remission for 24 weeks at Week 66 *among patients who were receiving corticosteroids at baseline*
- Change in CD signs and symptoms from baseline to Week 66 as assessed by the CD-PRO/SS measure

All secondary maintenance outcome measures are among patients who achieve CDAI-70 response at Week 14 unless otherwise stated.

Safety Outcome Measures

The safety outcome measures for this study are:

- Incidence and severity of adverse events
- Incidence of serious adverse events
- Incidence and severity of infection-related adverse events
- Incidence of infection-related serious adverse events
- Incidence and severity of injection-site reactions
- Incidence and severity of hypersensitivity reactions
- Incidence of adverse events leading to study drug discontinuation
- Incidence of specific laboratory abnormalities
- Incidence of malignancies
- Incidence of ATAs to etrolizumab

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are:

- Etrolizumab serum concentrations at *specified timepoints throughout the Induction and Maintenance Phases*

The PK outcome measures for the PK/PD substudy are:

- Observed maximum serum drug concentration (C_{max}) after the first and final doses during the Induction Phase
- Time to C_{max} after the first and final doses during the Induction Phase
- Area under the serum concentration–time curve (AUC) within a dose interval after the first and final doses during the Induction Phase

- Apparent clearance
- Apparent volume of distribution
- Elimination half-life

[redacted]

Investigational Medicinal Products

Test Product

Etrolizumab will be supplied by the Sponsor as a single-use PFS containing 150 mg/mL etrolizumab for SC administration. To preserve the blind to study drug assignment in the Induction Phase, all patients will receive injections from two PFSs at Weeks 0, 4, 8, and 12: a 1-mL PFS with a 0.7-mL injection volume (delivering placebo or 105 mg of etrolizumab) and a 2.25-mL PFS with a 1.4-mL injection volume (delivering placebo or 210 mg of etrolizumab). Depending on dose assignment, one PFS (patients assigned to active drug) or both PFSs (patients assigned to placebo) will contain placebo. At Week 2, all patients will receive a study drug injection from a 2.25-mL PFS with a 1.4-mL injection volume (delivering placebo or 210 mg of etrolizumab). The PFS will contain placebo for patients in the low-dose etrolizumab and placebo arms and active drug for patients in the high-dose etrolizumab arm. In the Maintenance Phase, patients will receive injections from a 1-mL PFS with a 0.7-mL injection volume (delivering placebo or 105 mg of etrolizumab).

Placebo

Drug product composition for the placebo is exactly the same as that of active drug product without the presence of etrolizumab.

Non-Investigational Medicinal Products

There are no protocol-mandated, non-investigational medicinal products.

Statistical Methods

Analyses of clinical remission will be made on the basis of patient-reported values for SF and AP (derived from the 7-day average scores), and centrally read, clinician-reported values for endoscopic improvement, as assessed by the SES–CD, the summed score of four endoscopic variables that are rated in 5 ileocolonic segments of the bowel

Primary Analysis

For the purpose of statistical analyses, the Induction and Maintenance Phases will be treated as independent studies.

Co-Primary Efficacy Endpoints

Induction Phase

- Proportion of patients in clinical remission at Week 14
- Proportion of patients achieving endoscopic improvement at Week 14

Maintenance Phase, *among patients who achieve CDAI-70 response at Week 14*

- Proportion of patients in clinical remission at Week 66
- Proportion of patients achieving endoscopic improvement at Week 66

Secondary Efficacy Endpoints

Induction Phase

- Proportion of patients who achieve clinical remission at Week 6
- Proportion of patients who achieve SES-CD ≤4 (≤2 for ileal patients), with no segment having a subcategory score (i.e., for ulceration size and extent, affected surface, or narrowing) that is >1, at Week 14
- Changes from baseline to Week 14 in CD-PRO/SS score

Maintenance Phase

- Proportion of patients in clinical remission at Week 66 among patients who achieve clinical remission at Week 14
- Proportion of patients who achieve corticosteroid-free clinical remission at Week 66
- Proportion of patients who maintain endoscopic improvement at Week 66 among patients achieving endoscopic improvement at Week 14
- Proportion of patients achieving SES−CD ≤4 (≤2 for ileal patients), with no segment having a subcategory score (i.e., for ulceration size and extent, affected surface, or narrowing) that is >1, at Week 66
- Proportion of patients achieving durable remission
- Proportion of patients achieving corticosteroid-free clinical remission for 24 weeks at Week 66
- Change from baseline to Week 66 in CD-PRO/SS score

Secondary endpoints for the Maintenance Phase will be assessed in the group of patients who were randomized into the Maintenance Phase, unless otherwise specified.

The primary induction study endpoint-analysis for Cohort 3 will evaluate the difference between each etrolizumab arm and placebo using the Cochran-Mantel-Haenszel (CMH) test statistic stratified by the factors used at randomization. The absolute treatment difference will be provided along with the 95% two-sided CI estimate.

The primary maintenance study endpoint-analysis will evaluate the difference in proportions between the two treatment arms using the CMH test statistic stratified by the factors used at randomization into the Maintenance Phase. The absolute treatment difference will be provided along with the 95% two-sided CI estimate. Detailed specifications of the statistical methods used for all analyses will be described in the SAP.

Determination of Sample Size

Induction Phase

A total of approximately 1150 patients will be randomized into one of three induction cohorts.

The pivotal analysis for induction phase will be performed using only patients from Cohort 3. In this pivotal induction cohort, patients will be randomized to receive either placebo, etrolizumab 105 mg or etrolizumab 210 mg in a 2:3:3 ratio. The co-primary endpoint will be tested using a CMH test at the 5% significance level, where both clinical remission and endoscopy improvement are required to be significant. The sample size for Cohort 3 is expected to provide ≥85% power to detect a ≥15% difference in rates of clinical remission (SF mean daily score ≤3 and AP mean daily score ≤1) between each etrolizumab arm and placebo under the assumption of a placebo remission rate of ≤15% and a two-sided test performed at a significance level of 5%. Additionally, Cohort 3 will provide ≥80% power to detect a 10% difference in proportions for each etrolizumab arm versus placebo for endoscopic improvement, under the assumption of placebo response rate of ≤5% and a two-sided test at the 5% significance level. The χ^2 test was used to confirm the power calculations.

Maintenance Phase

A total of approximately 480 patients achieving CDAI-70 response at Week 14 will be eligible to enroll into the Maintenance Phase.

A co-primary endpoint will be used for the analysis of the Maintenance Phase: clinical remission (SF mean daily score ≤ 3 and AP mean daily score ≤ 1) and endoscopic improvement at Week 66. The maintenance co-primary analysis will be performed on all patients re-randomized into the Maintenance Phase who were randomized to etrolizumab (105 mg or 210 mg) in the Induction Phase. The co-primary endpoint will be tested using a CMH test at the 5% significance level, where both clinical remission and endoscopy improvement are required to be significant. Note that to maintain the blind, patients randomized to placebo in the Induction Phase will undergo a sham randomization and will receive placebo in the Maintenance Phase. These patients will not form part of the pivotal maintenance analysis.

Of the approximately 480 patients projected to be enrolled in the Maintenance Phase, approximately 420 patients will undergo re-randomization to receive either placebo or etrolizumab, and approximately 60 patients will undergo a sham randomization to placebo. These projections are based on the assumption that 50% of patients receiving etrolizumab and 40% of patients receiving placebo during the Induction Phase will be eligible for the Maintenance Phase.

Assuming a maintenance sample size of *210* patients per arm using a 1:1 allocation to receive either placebo or etrolizumab 105 mg, the maintenance analyses conducted at the 5% significance level will provide the following power:

- Clinical remission at Week 66 (SF mean daily score ≤3 and AP mean daily score ≤1): at least 90% power to detect a 15% treatment difference assuming a placebo Week 66 remission rate of up to 20%
- Endoscopic improvement: *approximately* 90% power to detect a 15% treatment difference assuming a placebo Week 66 improvement rate of up to 30%

Furthermore, the study is designed to provide sufficient power for the following secondary analyses:

- Clinical remission at Week 66 among patients achieving clinical remission at Week 14: a sample size of N=*186* (i.e., *93* per arm) will provide 80% power to detect a 20% treatment difference assuming a placebo rate of up to 30%. This assumes a Week 14 clinical remission rate of ≥22% among etrolizumab patients.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
AIS	adenocarcinoma in situ
ANCOVA	analysis of covariance
AP	abdominal pain
APQ	Abdominal Pain Questionnaire
ATA	anti-therapeutic antibody
AUC	area under the serum concentration-time curve
AZA	azathioprine
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CD–PRO/SS	Crohn's Disease–Patient-Reported Outcome Signs and Symptoms
CIN	cervical intraepithelial neoplasia
C_{max}	maximum serum drug concentration
CMH	Cochran-Mantel-Haenszel
C_{min}	minimum serum drug concentration
[redacted]	[redacted]
CS	corticosteroid
CSF	cerebrospinal fluid
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
e-diary	electronic diary
EMA	European Medicines Agency
ePRO	electronic patient-reported outcome
[redacted]	[redacted]
FDA	U.S. Food and Drug Administration
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	health care professional
HCV	hepatitis C virus

Abbreviation	Definition
HIPAA	U.S. Health Insurance Portability and Accountability Act
[redacted]	[redacted]
HSIL	high-grade squamous intraepithelial lesion
IBD	inflammatory bowel disease
[redacted]	[redacted]
ICH	International Council for Harmonisation
iDCC	independent data coordinating center
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IR	inadequate responder
IRB	Institutional Review Board
IS	immunosuppressant
IV	intravenous
IxRS	interactive voice or Web-based response system
JCV	John Cunningham virus
LD	loading dose
mAb	monoclonal antibodies
MAdCAM-1	mucosal addressin cell adhesion molecule
mITT	modified intent to treat
MOA	mechanism of action
MS	multiple sclerosis
MRI	magnetic resonance imaging
MTX	methotrexate
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAIDs	nonsteroidal anti-inflammatory drugs
OLE	open-label extension
PD	pharmacodynamics
PFS	prefilled syringe
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PPD	purified protein derivative
PRO	patient-reported outcome
PRO2	Patient-Reported Outcome-2
Q4W	every 4 weeks

Abbreviation	Definition
QOL	quality of life
qPCR	quantitative polymerase chain reaction
RCR	Roche Clinical Repository
SC	subcutaneous
SES–CD	Simple Endoscopic Score for Crohn's Disease
SF	liquid/soft stool frequency
SM	safety monitoring
SUSAR	suspected unexpected serious adverse reaction
TB	Tuberculosis
TNF	tumor necrosis factor
TNF–IR	inadequate response to anti-tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON CROHN'S DISEASE

Crohn's disease (CD) is a chronic, relapsing form of inflammatory bowel disease (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. The disease course is variable; patients can experience a severe initial flare followed by few symptoms over the next 10 years (43%) or symptoms that are chronic and persistent (19%) or relapsing-remitting (32%) (Baumgart and Sandborn 2012).

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

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

Systemic corticosteroids (CSs) 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 CS dependent (Faubion et al. 2001; Peyrin-Biroulet et al. 2010). Even if patients' symptoms improve, fewer than 30% are expected to achieve endoscopic improvement with steroid treatment (Modigliani et al. 1990). The adverse effects of steroids are well documented and 50% of patients will stop their treatment because of this; long-term safety outcomes include osteoporosis, cataracts, and diabetes.

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

The development of monoclonal antibodies (mAbs) against tumor necrosis factor (TNF)–α (anti-TNFs) 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), possibly because of an underlying pathobiology that is not TNF-α driven and, as such, may benefit from a different mechanistic class of drug. It is estimated that 30%–40% of patients will be secondary non-responders (i.e., initially responsive) but lose response or become intolerant in their first year of treatment (Colombel et al. 2007). Secondary non-response has been attributed to the development of neutralizing antibodies, resulting in low drug serum levels, to accelerated drug clearance, or a biological escape mechanism that may benefit from a therapy with a different pharmacological target. 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 infusion reactions, occurring in 9%–17% of patients treated with infliximab (de Vries et al. 2011), and injection site reactions, occurring in 10% of patients receiving adalimumab (van der Heijde et al. 2006). Overall, the benefits versus risks are considered acceptable for this drug class, but there continues to be a need for treatments with better benefit-risk profiles that attenuate inflammation and the clinical sequelae and improve the long-term prognosis of patients with CD.

The anti-integrins are another class of biologics approved for the treatment of CD. Natalizumab is an anti-integrin approved in the U.S. only for the treatment of moderate to severely active CD. The use of natalizumab, which blocks both $\alpha4\beta1$ and $\alpha4\beta7$ has

been limited because of concerns that inhibition of $\alpha 4\beta 1$/VCAM-1 binding increases the risk of progressive multifocal leukoencephalopathy (PML), a rare but serious infection of the CNS. Vedolizumab is the most recently approved gut-selective anti-integrin for CD, but this targets only the $\alpha 4\beta 7$ integrin receptor, inhibiting T-lymphocyte binding to the adhesion molecule MAdCAM-1, and is administered as an intravenous (IV) infusion. In the pivotal trials for vedolizumab, 31% of patients had a clinical response with 6 weeks of induction treatment; up to 39% of the vedolizumab responders achieved remission with 46 weeks of maintenance treatment, compared with 22% of patients given placebo (Sandborn et al. 2013). While vedolizumab shows promise as a new treatment for CD, there remains a need for a more convenient therapy that is gut selective and achieves better response and remission rates.

1.2 BACKGROUND ON ETROLIZUMAB

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

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

It is important to note that, unlike natalizumab, etrolizumab does not bind to $\alpha 4\beta 1$ or inhibit the interaction of $\alpha 4\beta 1$ and VCAM-1 and the distribution and homing of lymphocytes to the CNS and peripheral lymphoid tissue (see Etrolizumab Investigator's Brochure). As such, etrolizumab is not expected to increase the risk of PML. However, in any clinical trial of etrolizumab, signs or symptoms suggestive of PML would be carefully monitored through regular neurological examinations. Safety assessments for etrolizumab have been completed in adult Phase I and Phase II studies, in which patients with moderate to severely active UC received either single or multiple doses of IV or subcutaneous (SC) etrolizumab. A total of 158 patients have been exposed to etrolizumab in the Phase I and II studies, with no significant adverse safety signals,

including any evidence of increased rates of serious or opportunistic infections that might be associated with etrolizumab treatment. Acknowledging that the clinical experience with etrolizumab is limited, no events of PML have been reported in patients treated with etrolizumab.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The purpose of this study is to assess the efficacy and safety of etrolizumab, a novel anti-integrin with a unique MOA that has been shown to inhibit the trafficking and retention of inflammatory T-cells in the intestinal mucosa via a disruption of $\alpha 4\beta 7$/MAdCAM-1 and $\alpha E\beta 7$/E-cadherin binding.

Although etrolizumab has not been studied in patients with CD, preliminary expression studies of the pharmacological target for etrolizumab, the integrin $\beta 7$ receptor, on gut CD4+ and CD8+ T cells isolated from resections of patients with UC and patients with CD 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 will 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 MOA of etrolizumab may bring enhanced efficacy in CD without generalized immunosuppression compared with available anti-integrin and anti-TNF therapies.

In a global Phase II study (Study ABS4986g; EUCALYPTUS), etrolizumab was efficacious in treating moderate to severe UC and achieved a placebo-corrected clinical remission rate of 20.5% ($p = 0.058$) and an endoscopic remission rate of 10.3% ($p = 0.004$) at 10 weeks after treatment initiation (105 mg every 4 weeks [Q4W]) in an all-comers population (Vermeire et al. 2013). In addition, etrolizumab had an acceptable safety profile with no clinically significant safety signals observed. There is no known safety risk identified for etrolizumab at this time, but as an investigational medicinal product (IMP) with limited Phase II data, the full safety profile for etrolizumab will be further characterized as Phase III clinical development progresses. A safety plan is provided in Section 5, describing potential risks for etrolizumab and the risk-mitigation strategies to minimize risks for the patients in this study.

To address potential risks to participating patients, the clinical experience with etrolizumab in patients with UC and information on the mechanism of action was considered in the clinical design and safety management plan of the proposed Phase III study to address potential risks to participating patients. The planned induction and maintenance dose regimens are expected to be safe and efficacious and were selected based on the observed safety, pharmacokinetic (PK), and pharmacodynamic (PD) profile of etrolizumab in UC, with consideration given to potential differences in exposure related to the transmural and patchy presentation of inflammation in CD. Only patients who have undergone a sufficient washout of prior biological therapy for CD will be

eligible to participate and patients with a history of moderate allergic reactions to mAbs will be excluded. As described in Section 1.2, etrolizumab is selective for intestinal mucosal tissue and does not impact peripheral lymphoid populations. Consequently, the risk of PML is expected to be lower with etrolizumab compared with other non-gut-selective biologics, with no events of PML reported in the UC Phase II or OLE studies. Patients at risk of severe infections (including PML and opportunistic infections) will be excluded from this study. The potential risk of severe infections associated with concomitant IS therapy has been carefully considered. On the basis of data from the UC Phase II study and the recent vedolizumab Phase III program, which showed that concomitant IS use did not impact the infection rates, concomitant IS use will not be prohibited in this study (see Section 3.3.3 for a more detailed assessment of this risk).

Patient safety will be monitored throughout the study via assessment of vital signs, safety laboratory assessments, neurological exams, and continuous review of adverse events. Should any patients become pregnant, develop anaphylaxis, develop PML, specific malignancy, colonic mucosal dysplasia, or certain specific serious infections (see Section 5.1.1.1), they will be permanently discontinued from the study treatment (see Section 4.6.2). Patients will not be eligible to enter the Induction Phase of the study if requiring a CS dose $>$20mg/day prednisone or equivalent, or $>$6 mg/day oral budesonide. In addition, the dose must have remained stable for 2 weeks prior to patient randomization into the Induction Phase. During the Maintenance Phase of the study, patients who experience a clinical relapse in their CD status will have the option to enroll into an open-label study of etrolizumab. During the Induction Phase, when concomitant CD treatments must remain stable, patients will not be allowed to participate if they require a CS dose $>$20mg/day prednisone or equivalent.

An independent Data Monitoring Committee (iDMC) will review all safety data twice yearly during the study or more frequently based on the emerging safety data. Refer to Section 5 for additional details.

Given 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 in a Phase III clinical trial in CD, supported by:

- Studies of an anti-$\alpha 4\beta 7$ mAb, vedolizumab, approved for the treatment of patients with moderate to severe CD
- Completed 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 CD program with robust safety monitoring

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

Analyses of clinical remission will be made on the basis of patient-reported values for liquid/soft stool frequency (SF) and abdominal pain (AP) (derived from the 7-day average scores), and centrally read, clinician-reported values for endoscopic improvement, as assessed by the Simple Endoscopic Score for Crohn's Disease (SES–CD), the summed score of four endoscopic variables that are rated in 5 ileocolonic segments of the bowel (Daperno et al. 2004).

2.1.1 Co-Primary Efficacy Objectives

The co-primary efficacy endpoints for this study are the following:

- Clinical remission, defined as a SF mean daily score $\leq$ 3 and an AP mean daily score $\leq$1 with no worsening in either subscore compared to baseline, averaged over the 7 days prior to visit
- Endoscopic improvement, defined as a $\geq$50% reduction from the baseline SES-CD

Primary efficacy objectives for this study will be analyzed separately for the Induction and Maintenance Phases as outlined below.

- Induction Phase: To independently evaluate the efficacy of etrolizumab dose regimens compared with placebo in inducing clinical remission and endoscopic improvement at the end of the Induction Phase (Week 14)
- Maintenance Phase: To independently evaluate the efficacy of etrolizumab compared with placebo in achieving clinical remission and endoscopic improvement at 1 year of maintenance treatment (Week 66), for patients who achieved a Crohn's Disease Activity Index (CDAI)–70 response (defined as a decrease of at least 70 points from baseline CDAI) at Week 14

2.1.2 Secondary Objectives

Induction Phase

- To evaluate the efficacy of etrolizumab compared with placebo in achieving clinical remission at Week 6
- To evaluate the efficacy of etrolizumab compared with placebo in achieving an SES-CD ≤4 (≤2 for ileal patients), with no segment having a subcategory score (i.e., for ulceration size and extent, affected surface, or narrowing) that is >1, at Week 14
- To evaluate the reduction in CD signs and symptoms achieved by etrolizumab dose regimens compared with placebo at Week 14 as assessed by the Crohn's Disease Patient-Reported Outcome Signs and Symptoms (CD–PRO/SS) measure

Maintenance Phase

All secondary Maintenance endpoints are for patients who achieved CDAI-70 at Week 14, unless otherwise stated.

- To evaluate the efficacy of etrolizumab compared with placebo in maintaining clinical remission at Week 66 for patients who achieved clinical remission at Week 14
- To evaluate the efficacy of etrolizumab compared with placebo in achieving corticosteroid-free clinical remission at Week 66 *among patients who were receiving corticosteroids at baseline*
- To evaluate the efficacy of etrolizumab compared with placebo in maintaining endoscopic improvement at Week 66 for patients who achieved endoscopic improvement at Week 14
- To evaluate the efficacy of etrolizumab compared with placebo in achieving a SES–CD ≤4 (≤2 for ileal patients), with no segment having a subcategory score (i.e., for ulceration size and extent, affected surface, or narrowing) that is >1, at Week 66
- To evaluate the efficacy of etrolizumab compared with placebo in achieving durable clinical remission during 1 year of maintenance therapy (i.e., at ≥4 of the 6 in-clinic assessment visits that are conducted during the Maintenance Phase at Weeks 24, 28, 32, 44, 56, and 66)
- To evaluate corticosteroid-free clinical remission at Week 66 (off corticosteroid for at least 24 weeks prior to Week 66) in patients who were receiving corticosteroids at baseline
- To evaluate change in CD signs and symptoms from baseline to Week 66 as assessed by the CD-PRO/SS measure

[redacted]

2.2 SAFETY OBJECTIVES

The safety objectives for this study are:

- To evaluate the overall safety and tolerability of etrolizumab compared with placebo during Induction and Maintenance Phases of therapy
- To evaluate the incidence and severity of infection-related adverse events
- To evaluate the incidence of malignancies
- To evaluate the incidence and severity of immunogenic responses (anti-therapeutic antibodies [ATAs])
- To evaluate the incidence and severity of hypersensitivity reaction events

2.3 PHARMACOKINETIC OBJECTIVES

The PK objectives for this study are:

- To evaluate etrolizumab serum concentrations *during* the Induction Phase (Week 14) and at several predose timepoints when at steady state during the Maintenance Phase in patients who are re-randomized to etrolizumab
- To characterize the interindividual variability and potential covariate effects on etrolizumab serum exposure
- To investigate the relationship between serum exposure and clinical response and remission as well as endoscopic changes during the induction and maintenance treatment phases
- To characterize the PK profile of etrolizumab in patients with CD and the relationship between serum exposure of etrolizumab and $\beta 7$ receptor occupancy by etrolizumab on peripheral blood T and B lymphocytes subsets (in a PK/PD substudy)

[redacted]

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is a multicenter, Phase III, double-blind, placebo-controlled study evaluating the efficacy, safety, and tolerability of etrolizumab compared with placebo during induction and maintenance treatment of moderate to severely active CD. Patients enrolled in this study may be eligible to participate in an open-label extension–safety monitoring (OLE-SM) study (GA29145), which consists of two parts: Part 1 (designated OLE [open-label extension]) and Part 2 (designated SM [safety monitoring]).

The study design will consist of 1) a Screening Phase (up to 35 days) to determine patients' eligibility for the study, 2) an Induction Phase (14 weeks), followed by 3) a Maintenance Phase (52 weeks) in patients demonstrating a CDAI-70 response (see Table 1) at the end of the Induction Phase, and 4) a Safety Follow-Up Phase (12 weeks) after administration of the last dose of study drug in the Maintenance Phase for those patients who do not participate in Part 1 (OLE) of Study GA29145 (see Figure 1 and Figure 2). At the completion of the Safety Follow-Up Phase, patients will be asked to enter an extended PML-monitoring phase Part 2 (SM) of Study GA29145 for 92 weeks. An independent Data Monitoring Committee (iDMC) will monitor safety and study conduct on an ongoing basis (Refer to Section 5.1.1 for details of the iDMC).

Patients in all cohorts will be required to provide blood samples for population PK analysis and PD characterization (see Appendix 1a and Appendix 1b). Patients will also have an option to consent and participate in a PK/PD substudy. The objective of the substudy is to determine the relationship between etrolizumab exposure and receptor occupancy in peripheral blood in patients with CD. To achieve this objective, it is planned that approximately 150 *evaluable* patients will be enrolled in the substudy (see Section 3.3.8). Blood sampling for the PK/PD substudy will continue in the Maintenance Phase.

Moderate to severely active CD will be defined at baseline by clinical signs and symptoms that result in a CDAI score between ≥220 and ≤480, as well as either an average SF ≥6 or an average SF >3 and average AP >1, calculated on the day of randomization using electronic diary (e-diary) PRO data from the 7 days prior to randomization. In conjunction, the presence of active inflammation, defined as a SES-CD of ≥7, or ≥4 in cases of isolated ileitis or post-ileocecal resection, is required and will be determined by a screening ileocolonoscopy scored using the central read model.

The study population will consist of patients who are refractory or intolerant to one or more of the following therapies: 1) CS, 2) IS, or 3) anti-TNFs (or TNF-IR). Patients who enroll on the basis of refractory or intolerance to CS and/or IS may have been previously exposed to ant-TNFs or be naïve to anti-TNFs (as defined in Section 4.1.1).

Approximately 1150 patients will be randomized into the study from approximately *500* global investigational sites via enrollment into one of three cohorts (see Section 3.1.3). The enrollment will be sequential, first into Cohort 1, then Cohort 2, and lastly Cohort 3.

3.1.2 Overview of Screening Phase

Patients will be evaluated for eligibility in the 35-day Screening Phase (see Figure 1). Assessments for eligibility are noted in Appendix 1a.

During the Screening Phase, patients taking CS therapy must have been on a stable dose of ≤20 mg/day prednisone or equivalent or ≤6 mg/day oral budesonide for at least 2 weeks immediately prior to their randomization. Similarly, eligible patients requiring background IS therapy (e.g., AZA *[or equivalent]*, 6-MP *[or equivalent]*, or MTX) must be receiving a stable IS dose regimen for at least 8 weeks immediately prior to their randomization. Patients who have been treated with anti-TNF therapy must have discontinued this treatment for at least 8 weeks prior to their randomization.

The ileocolonoscopy should be performed during the Screening Phase and at least 9 days prior to randomization to allow sufficient time for a central reader scoring and determination of eligibility, and to avoid the ileocolonoscopy bowel preparation influencing the patient reported outcomes used in the determination of baseline SF, AP, and CDAI scores (i.e., abdominal pain, general well-being, and stool frequency).

Refer to Section 4.5.2.1 for requirements related to re-screening a patient.

3.1.3 Number of Patients

Approximately 1150 patients will be randomized into the Induction Phase of the trial via enrollment into one of three cohorts (see Section 3.1.3 and Table 4 for details regarding sample size for each cohort).

Patients receiving etrolizumab in the Induction Phase who achieve a CDAI-70 response at Week 14 without the use of rescue therapy will be randomized into the Maintenance Phase of the trial *until a sample size of approximately 480 patients enrolled in the Maintenance Phase is achieved. Of the approximately 480 patients enrolled in the Maintenance Phase, approximately 420 patients are estimated to be CDAI-70 responders who received etrolizumab during the Induction Phase and will be re-randomized to either etrolizumab 105 mg SC Q4W or placebo in the Maintenance Phase. The remaining approximately 60 patients are CDAI-70 responders who received placebo during the Induction Phase and will undergo a sham randomization to blinded placebo treatment during the Maintenance Phase.*

3.1.4 Overview of Induction Phase

Eligible patients will be enrolled sequentially into one of three cohorts for the 14-week Induction Phase (see Appendix 1a).

Patients enrolled in Cohort 1 (double-blind, placebo-controlled, exploratory cohort; n =300) will be randomized in a 1:2:2 ratio to receive placebo, etrolizumab 105 mg SC Q4W (low dose), or etrolizumab 210 mg SC (high dose) at Weeks 0, 2, 4, 8, and 12 within a 14-week Induction Phase (note that patients randomized to low-dose etrolizumab and patients randomized to placebo will receive one placebo injection at Week 2, see below). Patients enrolled in Cohort 2 (etrolizumab dose–blind, active-treatment cohort; n =350) will be randomized in a 1:1 ratio to receive low-dose or high-dose regimens of etrolizumab. Patients enrolled in Cohort 3 (double-blind, placebo-controlled, pivotal cohort; n =500) will be randomized in a 2:3:3 ratio to receive placebo or etrolizumab low-dose or high-dose. Because the low dose and high dose of etrolizumab are in syringes of different volumes, in order to preserve the blind, patients in all three cohorts will receive two injections at Weeks 0, 4, 8, and 12. Patients randomized to low-dose etrolizumab will receive one placebo (matching high-dose prefilled syringe) and one low-dose etrolizumab injection at each administration except at Week 2, when they will receive one placebo injection. Patients randomized to high-dose etrolizumab will receive one placebo and one high-dose etrolizumab injection at each administration, except at Week 2 where they will receive one high-dose injection. Finally, patients randomized to placebo will receive two placebo injections at every administration, except at Week 2 where they will receive one placebo injection.

The randomization in all cohorts will be stratified by concomitant oral CS treatment (yes vs. no), concomitant IS treatment (yes vs. no), baseline CDAI ≤330 (yes vs. no), and prior anti-TNF exposure (yes vs. no). The enrollment will be managed to ensure that the proportion of the TNF-exposed patients in Cohort 3 does not exceed approximately 60% and that the proportion of patients with a CDAI score between >450 and ≤480 does not exceed approximately 10% in each cohort.

During the Induction Phase, patients in all cohorts should keep their dose(s) of CS and IS therapy stable (if requiring CS/IS at baseline). Increase in dose of these medications

will be considered rescue therapy (refer to Section 4.4.4.1 for definitions of rescue therapy). Also, every attempt should be made to keep anti-diarrheal medication at a fixed dose, if required. The impact of titrating anti-diarrheal medication on the placebo response rate for SF and AP has not been studied in a moderate to severely active CD population; dose adjustments may confound the data interpretation. Changes to any concomitant medications must be documented in the electronic Case Report Form (eCRF). Refer to Section 4.4.1 for details of the management of concomitant CD medications.

Between and including Weeks 10 and 14, there is an optional escape to Part 1 (OLE) of Study GA29145, where patients can receive open-label etrolizumab. This can only be exercised if a patient experiences disease worsening, defined as a CDAI Week 10 score greater than the patient's baseline (Week 0) score.

At Week 14, patients achieving CDAI-70 response without the use of rescue therapy will continue to the Maintenance Phase *until a sample size of approximately 480 patients enrolled in the Maintenance Phase has been achieved*. Patients not eligible for the Maintenance Phase may be eligible for Part 1 (OLE) of Study GA29145 *(see Section 4.5.9)*.

Patients who are in the Induction Phase after closure of enrollment into the Maintenance Phase may enroll in Part 1 (OLE) of Study GA29145, if eligible, upon completion of the Induction Phase at Week 14 or in the event of disease worsening, as specified above, between Weeks 10 and 14 (see Section 4.5.9).

Patients who require surgical intervention for CD at any time during the Induction Phase will stop study treatment, enter the Safety Follow-Up Phase, and will be asked to enter Part 2 (SM) of Study GA29145 for PML monitoring. Patients who self-withdraw from the Induction Phase and do not meet the eligibility criteria for OLE treatment (see Section 4.5.9) will also enter the Safety Follow-Up Phase and be asked to enter Part 2 (SM) of Study GA29145 for PML monitoring.

3.1.5 Overview of Maintenance Phase

At the end of the Induction Phase (Week 14), patients will be assessed for a CDAI score and will undergo a full endoscopy (ileocolonoscopy) with central reading to determine an SES–CD. Every attempt must be made to schedule the ileocolonoscopy to take place at the Week 14 visit or no later than 5 calendar days after this visit; the procedure must not be scheduled before Week 14. The patient-reported outcomes e-diary data (i.e., abdominal pain, general well-being, and stool frequency) that are captured in the 7 days prior to the bowel preparation will be used to calculate the Week 14 SF, AP, and CDAI scores, thus removing any influence of the bowel preparation on these outcomes.

Patients who received placebo during the Induction Phase and achieved a CDAI-70 response will undergo a sham randomization to blinded placebo maintenance treatment, and patients who received etrolizumab and achieved a CDAI-70 response at Week 14

without the use of rescue therapy will be randomized into the Maintenance Phase in a 1:1 ratio to treatment with placebo or etrolizumab 105 mg SC Q4W (see Figure 2). *This will continue until a sample size of approximately 480 patients enrolled in the Maintenance Phase has been achieved.*

The randomization call may take place between Week 14 (last visit in the Induction Phase) and Week 16, provided the patient has been assessed as eligible for the Maintenance Phase. The randomization will be stratified by CDAI remission at both Weeks 10 and 14 (yes vs. no), induction dose regimen (low dose vs. high dose), concomitant oral CS treatment (yes vs. no), and prior anti-TNF exposure (yes vs. no). The first dose in the Maintenance Phase is administered at the Week 16 clinic visit.

Patients should remain on a stable dose of IS therapy throughout the treatment period, unless dose reduction or discontinuation is required because of a toxicity related to the medication (see Section 4.4.2 for more details). CS dose should be tapered starting at Week 14 see Section 4.4.3). Patients who cannot tolerate the CS taper without recurrence of CD symptoms or symptoms of steroid withdrawal can receive an increase in CS dose, but this should not exceed the dose administered at randomization. The dose-tapering regimen must be re-initiated within 2 weeks.

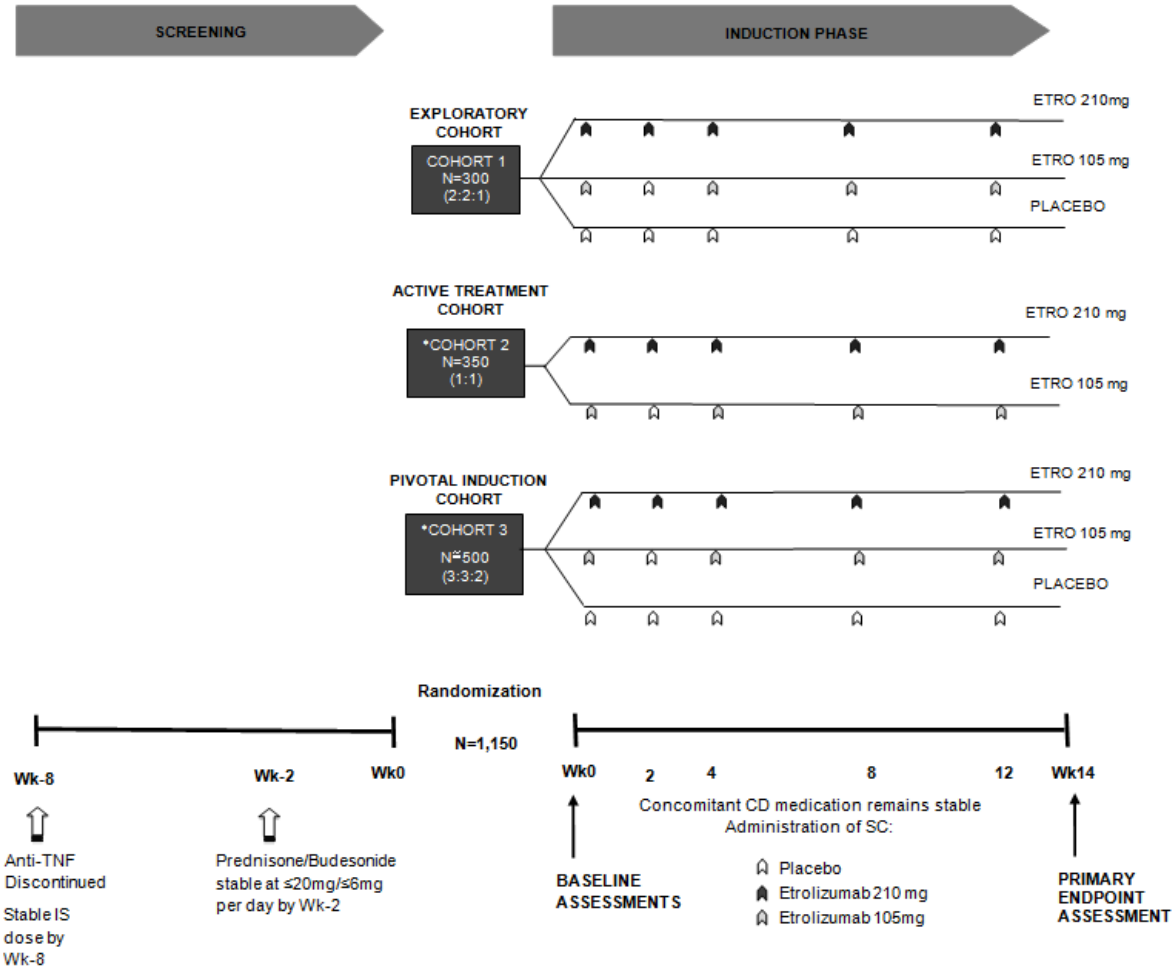
During the Maintenance Phase, patients who experience a clinical relapse may have the option of escaping to Part 1 (OLE) of Study GA29145. Clinical relapse is defined as meeting at least one of the following criteria on two consecutive visits (may include unscheduled visits), with at least one of the two consecutive CDAI scores ≥220:

- CDAI score ≥ the baseline (Week 0) score
- CDAI score ≥100 points higher than the Week 14 score

All patients who complete their final Maintenance Phase visit at Week 66 may be eligible to enroll in Part 1 (OLE) of Study GA29145. Patients who do not enroll in Part 1 (OLE) will enter a 12-week Safety Follow-Up Phase, after which they will be asked to enroll in a 92-week extended PML-monitoring phase (Part 2 [SM] of Study GA29145). Patients who require surgical intervention for CD at any time during the Maintenance Phase will stop study treatment, enter the Safety Follow-Up Phase, and will be asked to enter Part 2 (SM) of Study GA29145 for PML monitoring. Patients who self-withdraw from the Maintenance Phase and do not meet the eligibility criteria for OLE treatment (see Section 4.5.9) will also enter the Safety Follow-Up Phase and be asked to enter Part 2 (SM) of Study GA29145 for PML monitoring.

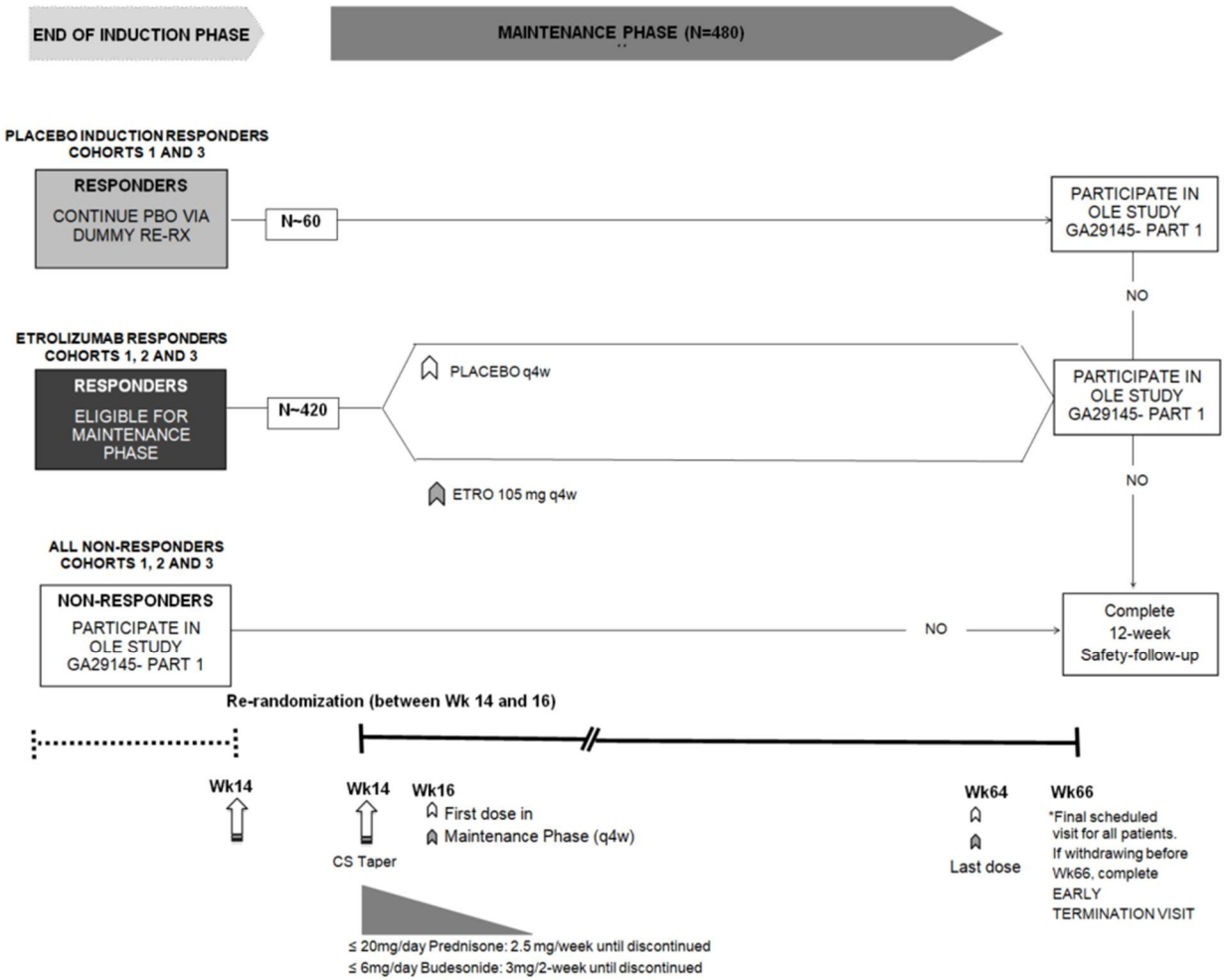
Patients who withdraw will complete the early withdrawal assessments listed in the Schedule of Assessments; withdrawn patients will not be replaced.

Figure 1 Study Schema Induction Phase



Anti-TNF = anti-tumor necrosis factor; CD = Crohn's disease; ETRO = Etrolizumab; IS = immunosuppressants, SC = subcutaneous; Wk = week.

Figure 2 Study Schema Maintenance Phase



CS = corticosteroids; ETRO = Etrolizumab; OLE = open label extension phase; PBO = placebo; q4w = every 4 weeks; Re-Rx = re-randomized; Wk = week.

3.2 END OF STUDY

Length of Study

The study duration, from screening to end of study participation for a given eligible patient, will be up to 82 weeks (4-week screening period + 14-week Induction Phase + 52-week Maintenance Phase + 12-week Safety Follow-up Phase). The total length of the treatment period will be 66 weeks (14-weeks Induction Phase + 52-week Maintenance Phase).

Those who do not enroll in Part 1 (OLE) of Study GA29145 will continue to 12 weeks of safety follow-up in this study and then be asked to enroll in Part 2 (SM) of Study GA29145 for 92 weeks of monitoring for PML.

End of Study

The end of the study is defined as *meeting one of the following criteria, whichever is later:*

- *Completion of the 12-week Safety Follow-up Phase for the last patient in the Induction Phase*
- The final visit for the last *Induction* patient transferred to Part 1 (OLE) of Study GA29145
- *Completion of the 12-week Safety Follow-up Phase for the last patient in the Maintenance Phase*
- *The final visit for the last Maintenance patient transferred to Part 1 (OLE) of Study GA29145*

3.3 RATIONALE FOR STUDY DESIGN

This study is a multicenter, randomized, double-blind, parallel-group comparison of etrolizumab and placebo. As recommended by the European Medicines Agency (EMA) new medicinal products guideline for CD (CPMP/EWP/2284/99 Rev. 1) and as employed in U.S. Food and Drug Administration (FDA)-approved registration trials of CD therapies, this study combines induction and maintenance therapy in a re-randomization/withdrawal design to assess the efficacy and safety of etrolizumab treatment for induction and maintenance of remission.

3.3.1 Rationale for the Primary and Key Secondary Study Endpoints

The pivotal cohort of this study is designed to assess remission of signs and symptoms as well as endoscopic improvement as co-primary outcome measures in CD.

Clinical remission is defined as the mean number of liquid/soft stools for the 7 days prior to the assessment visit (SF) being ≤3 and the mean AP score (on a 0–3 scale) with no worsening in either subscore compared to baseline, for the 7 days prior to the assessment visit (AP) being ≤1.

The primary *clinical* endpoint is based on previous FDA recommendations, the evolving global regulatory environment (new EMA new medicinal products guideline for CD released July *2018*; CHMP 2016), and the results generated from the exploratory induction of Cohort 1 in this study. Both FDA and EMA in its new guideline discouraged the use of CDAI as primary endpoint for CD registration studies due to the limitations of the index. Instead, co-primary endpoint composed of patient-reported signs/symptoms and endoscopic measure is encouraged.

The use of SF and AP addresses the FDA's recommendation to use 7-day scores of SF and AP that correlate with CDAI remission. Defining clinical remission and response that use unweighted measures of AP and SF are more easily interpretable by clinicians, patients, and caregivers and are more likely to represent clinically meaningful improvements in symptoms and disease activity for moderate to severe CD patients experiencing different degrees of SF and AP during a flare.

Endoscopic improvement, defined as a change in SES-CD $\geq$50% from the baseline score (Ferrante et al. 2013), is a co-primary endpoint.

The SES−CD consists of four endoscopic variables (ulcers, ulcerated surface, inflamed surface, and presence of narrowings) that are scored in five ileocolonic segments. The SES−CD was prospectively developed and validated in patients with mild to severe CD (according to CDAI) by Daperno et al. (2004). This scoring system was recommended by the FDA and is generally preferred by physicians to other measures because of quantification of ulcer size (rather than a qualitative assessment of ulcer characteristics), determination of the percent ulceration in a segment (rather than determination by a visual analogue scale), and for better inter-rater reliability (inter-class correlation coefficients were 0.83 and 0.71 for SES−CD and Crohn's Disease Endoscopic Index of Severity (CDEIS), respectively; Khanna et al. 2014). Because the score does not adjust for the number of visible segments, only segments visualized at baseline will be included in the endpoint assessment. This means any new narrowing due to inflammation that renders a segment not evaluable for scoring after study treatment will qualify the patient as not achieving endoscopic improvement for the secondary endpoint analysis. Similarly, any improvement in inflammation that renders a segment evaluable for scoring after study treatment will not be reflected in the endpoint assessment. The Statistical Analysis Plan will describe any sensitivity analysis which are planned to assess the impact of these missing data on the endpoint. Given the limited experience with endoscopic scoring systems in general gastroenterology practice, all ileocolonoscopies in the study will be recorded at the investigational site, but central readers will determine the SES−CD.

Published studies have used multiple endoscopic endpoints to assess efficacy, which appear to be arbitrarily defined. Mucosal healing, defined qualitatively as an absence of mucosal ulcers, has been studied as a primary or secondary endpoint in a number of Phase IV studies (Rutgeerts et al. 2004 [natalizumab]; Rutgeerts et al. 2006 [infliximab];

Colombel et al. 2010 [infliximab and azathioprine]; Hebuterne et al. 2013 [certolizumab]; Rutgeerts et al. 2012 [adalimumab]). Some studies have defined endoscopic thresholds that represent endoscopic remission without clarity on the clinical significance of these scores (Hebuterne et al. 2013 [certolizumab]; Rutgeerts et al. 2012 [adalimumab]). In this study, endoscopic improvement is defined as the proportion of patients demonstrating a $\geq$50% reduction in SES-CD versus their pretreatment baseline score. For induction, this endpoint will be measured at Week 14 and, for maintenance, at Week 66 among patients who achieved a clinical response at Week 14. The endpoint is based on recent post hoc analyses of the SONIC trial which determined a $\geq$50% reduction in SES–CD score to be predictive of CS-free CDAI remission following 50 weeks of treatment with biologic therapy (Ferrante et al. 2013). This definition is also appropriate when considering the large variability in SES–CD change at the end of a 6-week Induction Phase measured in a sample of 24 placebo patients (with moderate to severely active CD) who were participating in one of two trials of novel biologic agents (Ferrante et al. 2010). The dataset showed that 6 patients achieved both 50% reduction in either SES–CD or CDEIS score, and at least a 5-point reduction in either SES–CD or CDEIS score.

3.3.2 Rationale for Patient Population

Patients with uncontrolled, moderate to severely active CD are at risk for developing stricturing or penetrating complications of inflammation, as well as symptoms that are debilitating to quality of life. The treatment goals for CD are to induce and maintain symptom improvement, induce mucosal healing, and improve quality of life. However, for a significant proportion of patients, these goals are not met by current therapies (see Section 1.1). As such, the study population will include patients who are refractory to one or more of the following therapies: 1) CS, 2) IS, or 3) anti-TNFs (or TNF-IR). Patients who enroll on the basis of refractory or intolerance to CS and/or IS may have been previously exposed to ant-TNFs or be naïve to anti-TNFs. Data from the etrolizumab Studies ABS4986g and GA27927 in UC (see Etrolizumab Iinvestigator's Brochure) and the vedolizumab GEMINI 2 and 3 studies (Sandborn et al. 2013; Sands et al. 2014) have demonstrated the favorable efficacy of the anti-$\alpha 4\beta 7$ mechanism of action in these patient subgroups. Patients belonging to each subgroup will be identified on the basis of refractory and inadequate-response criteria agreed upon with the EMA and FDA.

Patients with moderate to severely active CD between the ages of 18 and 80 years of age will be studied. This age range is typical of patients enrolled in clinical trials of new investigational agents for CD and reflects the observation that adult CD can become or persist as moderate to severely active disease at any age. Given that the primary clearance mechanism for etrolizumab is neither renal elimination nor first-pass metabolism, the risk of accumulation in patients $>$65 years of age is considered low and is also mitigated by laboratory exclusions related to poor renal and hepatic function.

In line with EMA guidelines, eligible patients must have an established diagnosis of CD for at least 3 months, with moderately to severely active disease corroborated by endoscopic evidence of inflammation. This is expected to improve the specificity of the CDAI, SF, and AP assessments and to allow the evaluation of endoscopic improvement endpoint. On the basis of the construction of the SES-CD, patients with isolated ileitis or post-ileocecal resection can be expected to have a lower baseline score compared with patients with ileocolonic disease, regardless of whether the extent of inflammation and ulceration is the same in affected segments. As such, different SES-CD entry scores are proposed for these subgroups of patients. It is acknowledged that patients with fistulizing disease are not well served by therapeutic options. [redacted]

3.3.3 Rationale for the Design of Induction and Maintenance Phases

Patient randomization into the Induction Phase will be stratified by disease activity on the basis of CDAI score ≤ 330 or > 330 (predictive of CDAI response and remission rates with biologic therapy; Sandborn et al. 2013; Sands et al. 2014), CS use, IS use, and prior anti-TNF failure (all indicators of disease activity). These factors are considered sufficient to mitigate the risk of imbalance in disease severity across treatment arms.

Assessment of the induction of clinical remission and endoscopic improvement at Week 14 is justified on the basis of the observation that anti-integrin therapies have a slower onset of action compared with anti-TNF therapies (Sandborn et al. 2005, 2013), as well as the clinical consensus that the onset of endoscopic improvement is typically observed 16–24 weeks after induction therapy, particularly in treatment refractory patients (a consensus supported by observed data showing that Mayo Clinic Score remission with etrolizumab took up to 14 weeks in TNF–IR patients with UC, see Etrolizumab Investigator's Brochure). A challenge of the 14-week Induction Phase is the requirement to keep concomitant CD therapies stable for the duration, so as not to confound the endpoint analysis. This is problematic in the context of patients who require rescue therapy to treat a flare and patients who are responding to treatment but unable to taper their CS dose. The study design addresses this by allowing use of rescue therapy in case of disease worsening, in which case patients would be classified as non-responders for the primary analysis, and restricting the maximum baseline CS to ≤ 20mg/day prednisone-equivalent dose. Although not prohibited therapeutic adjustment, increasing the dose of anti-diarrheal drugs should be avoided. Patients should keep their dose of anti-diarrheal medication stable as much as possible because the effect of titrating anti-diarrheal medication on the placebo-response rate on clinical remission is unknown.

The Induction Phase includes an exploratory cohort (Cohort 1) that is adequately sized to assess effect size and accuracy of statistical planning assumptions for the new endpoints in pivotal cohort (Cohort 3), the clinical validity of the dichotomous endpoint definitions, and the testing hierarchy of the endpoints. An active-treatment induction

cohort (Cohort 2) is also included in this study to generate a sufficient number of remitters for assessment of endpoints in the Maintenance Phase. The final cohort (Cohort 3) is a pivotal induction cohort, which will generate data for the endpoint analysis of the induction study.

Patients achieving a CDAI-70 response at Week 14 without rescue therapy will be re-randomized into the Maintenance Phase *until a sample size of approximately 480 patients in the Maintenance Phase is achieved*. Based on expert clinical opinion, patients achieving clinical remission and endoscopic improvement at Week 14 are expected to be a subpopulation within this group. Randomization into the Maintenance Phase will be stratified by the use of disease activity (described for the Induction Phase, except CDAI-remission [score <150] at both Weeks 10 and 14 will be used instead of CDAI ≤ 330 or >330). In addition, the randomization will be stratified by assignment to low- or high-dose etrolizumab (allowing an assessment of the impact of low- or high-dose induction therapy on the maintenance endpoints). Given the large number of strata, any potential imbalance in the proportion of endoscopic improvers at Week 14 will be handled using a covariate-adjusted analysis for the Week 66 endoscopic-improvement endpoint.

The duration of the Maintenance Phase (52 weeks) is considered an appropriate period by the FDA and EMA to establish the benefit of long-term therapy. During the first 8 weeks of the Maintenance Phase, patients receiving CS during the Induction Phase should undergo weekly dose reductions aligned with recommendations for CS tapering in the current American College of Gastroenterology and European Crohn's and Colitis Organization guidelines and following the EMA recommendation to avoid a rapid taper. The tapering schedule will allow patients to be assessed for the key secondary outcome of achieving corticosteroid-free clinical remission at Week 66 among patients who enter into maintenance phase.

An analysis of data from Study ABS4986g in patients with UC, which compared etrolizumab induction therapy with placebo (Vermeire et al. 2013), showed that infection rates were similar between etrolizumab and placebo in the subgroups of patients taking concomitant IS or CS therapy and the subgroups not taking these concomitant treatments (see Etrolizumab Investigator's Brochure). Although this is a small dataset with limited duration of exposure, more data for a longer duration of concomitant exposure are available for vedolizumab. A recent analysis of the vedolizumab development program demonstrated a modest increase in infection rates in patients using IS regardless of whether they received vedolizumab or placebo. In addition, the rates of infection and serious infection in the vedolizumab treatment group were similar in patients who were taking concurrent IS and those who were not (Colombel et al. 2016).

The risk of PML is expected to be lower with etrolizumab compared with other non-gut-selective biologics, with no events of PML reported in the UC Phase II or OLE

studies. However, the potential risk of PML and other severe infections has been carefully considered. Patient safety will be monitored throughout the study via assessment of vital signs, safety laboratory assessments, neurological exams, and continuous review of adverse events. Should any patients have anaphylaxis, develop PML, specific malignancy, colonic mucosal dysplasia, or certain specific serious infections, they will be permanently discontinued from the study treatment (Section 4.6.2). During the Maintenance Phase of the study, patients who experience a clinical relapse in their CD status will have the option to enroll into an open-label study of etrolizumab.

After the final visit in the treatment period, patients not participating in the OLE study will be assessed for safety for an additional 12 weeks starting after the last dose of study drug (see Section 4.5.8). This period reflects an adequate timeframe for washout of etrolizumab based on the estimated elimination half-life of 11 days (see Etrolizumab Investigator's Brochure).

3.3.4 Rationale for Etrolizumab Dose and Schedule

The PK profiles of several biologics are shown to be similar in UC and CD patient populations (Ternant et al. 2008, Fasanamde et al. 2009, Awni et al. 2013, Feagan et al. 2013; Sandborn et al. 2013). With these similarities, most biologic agents (e.g., anti-TNF or anti-integrin agents) have been successful in managing either UC or CD with use of the same dosing regimen (Feagan et al. 2013, Sandborn et al. 2013, Infliximab Package Insert; Adalimumab Package Insert). Because etrolizumab has been evaluated in patients with moderate to severely active UC in a Phase II study (Study ABS4986g; Eucalyptus) in which clinically meaningful induction of disease remission was achieved at a nominal dose of 100 mg (0.7 mL 150 mg/mL etrolizumab formulation) Q4W (three doses at Weeks 0, 4, and 8) and a nominal dose of 300 mg Q4W + loading dose(LD [LD of 420 mg at Week 0, 300 mg at Weeks 2, 4, and 8]) without significant safety concerns, the dose regimen (105 mg SC Q4W) of etrolizumab is also proposed as one of the doses to be tested in this study.

3.3.4.1 Rationale for Dose Ranging in the Induction Phase

In the Induction Phase, patients will be randomized to receive placebo, low-dose etrolizumab, or high-dose etrolizumab. Low-dose etrolizumab (105 mg) will be administered Q4W SC (Weeks 0, 4, 8, and 12).

A low dose regimen of 105 mg SC at Q4W is specified for dose ranging in the Induction Phase on the basis of the following considerations:

- In the Phase II UC trial, a nominal dose of 100 mg (0.7 mL of 150 mg/mL solution via vial and syringe), administered Q4W SC, showed a clinically meaningful induction of remission in patients with UC and had a favorable safety profile in the Phase II trial.

- The exposure of 100 mg, administered Q4W SC, was shown to be sufficient for maximal β7-receptor occupancy in both blood and colonic tissue from all patients who provided evaluable samples in the Phase II trial.
- Population PK/PD modeling predicts that a dose lower than the 100-mg SC Q4W regimen (e.g., 50 mg Q4W SC) will result in the loss of maximal β7-receptor occupancy during the Q4W dosing interval in approximately 44% of patients, and exposure is likely to be in the nonlinear PK range.

In addition to the 105-mg Q4W dose, a higher dose regimen of 210 mg SC at Weeks 0, 2, 4, 8, and 12 is specified for dose ranging in the Induction Phase on the basis of the following considerations:

- Despite the similarities in pathogenesis to UC, CD exhibits a more complex anatomical disease presentation throughout the gastrointestinal (GI) tract (i.e., transmural inflammation, patchy distribution, and strictures) when compared with UC. A positive exposure-response relationship was reported recently for vedolizumab, an in-class, anti-integrin antibody, following the Induction Phase of a Phase III clinical trial in patients with CD. Results showed the induction dose is sufficient to reach a complete receptor occupancy in all patients (Rosario et al. 2013), yet an increase in clinical response/remission was observed in patients with higher drug concentrations (Sandborn et al. 2013; Rosario et al. 2014). These observations from vedolizumab studies suggest that higher etrolizumab exposure may have the potential to offer more clinical benefit in this patient population.
- In addition to Q4W dose of 210 mg, the additional 210-mg dose at Week 2 is intended to load the etrolizumab exposure upfront to allow exposure achieving steady state faster. Earlier loading dose of anti-TNF agents or anti-integrins antibodies (Rutgeerts et al. 2004) were found to be effective in inducing clinical remission (CDAI score <150), and such a loading dose strategy was also implemented in this study.
- The proposed higher dose of 210 mg $\times$ 5 doses SC (at Weeks 0, 2, 4, 8, and 12) in patients with CD will result in a 2.5-fold total dose separation from the 105 mg Q4W $\times$ 4 dose regimen and is predicted to achieve an exposure level 30% lower than that from the 300 mg + 420 mg LD cohort studied in the UC Phase II trial, which had an acceptable safety/tolerability profile.

In summary, given the favorable safety profile and positive clinical outcomes observed in the nominal 100-mg Q4W cohort in etrolizumab UC Phase II study, it is appropriate to evaluate the 105-mg Q4W dose, the same regimen studied in the UC Phase III trials for CD induction therapy. In addition, given the complex pathophysiology of CD, an observed positive exposure-efficacy relationship for vedolizumab treatment despite a full receptor saturation in the blood, the available safety coverage and an acceptable safety profile of etrolizumab, it is scientifically sound to evaluate a higher dose regimen of 210 mg (Weeks 0, 2, 4, 8, and 12) to understand the dose-response relationship in patients with CD during the Induction Phase.

3.3.4.2 Rationale for Maintenance Dose Regimen

Patients who respond to etrolizumab treatment in the Induction Phase (see Table 1 for definition of CDAI-70 response) will be re-randomized to receive 105 mg etrolizumab or placebo Q4W in the Maintenance Phase; patients who respond to placebo in the Induction Phase will continue to receive placebo in the Maintenance Phase.

With the assumption that the PK profiles of mAbs (anti-TNF or anti-integrins) are similar in UC and CD patient populations (Ternant et al. 2008; Fasanamde et al. 2009; Awni et al. 2013; Feagan et al. 2013; Sandborn et al. 2013), the lower regimen of 105 mg SC at Q4W is specified in the Maintenance Phase on the basis the following considerations:

- The 105-mg Q4W SC dose planned for the Phase III study in CD is anticipated (by population modeling) to maintain full β7–receptor occupancy at all times in >85% of patients. The nominal dose of 100 mg Q4W SC administered in the UC Phase II study demonstrated an acceptable safety profile.
- The in-class anti-integrin vedolizumab was successful in maintaining remission with an every-8-week regimen that provided an average steady-state trough serum concentration sufficient to maintain maximal receptor occupancy (Rosario et al. 2013; Sandborn et al. 2013).

3.3.5 Rationale for Control Group

A placebo-treated control group will be used in this study to assess the differences in efficacy, safety, and tolerability in patients who receive etrolizumab and background CD therapy compared with patients who receive placebo and background CD therapy. The use of a control group is necessary given the inherent variability in disease flares and the use of subjective assessments, such as the PROs. Patients in the control group will undergo the same study assessments as the etrolizumab-treated patients. The 1:1 ratio for etrolizumab to placebo treated patients is necessary to achieve a statistically powered comparison of primary endpoint between these treatment arms.

[redacted]

3.3.8 Rationale for Pharmacokinetic/Pharmacodynamic Substudy Design

This protocol includes an optional PK/PD substudy to allow characterization of the relationship between etrolizumab exposure and occupancy of the β7 expressing cells in the blood in CD patients. These data will be used to characterize time course of etrolizumab serum concentration and its relationship with peripheral blood receptor occupancy in CD patients and help to identify the serum concentration (and potential variability) required for maintaining receptor occupancy in CD patients. These data are also essential for a full characterization of etrolizumab PK (establishing a basic PK structural model) in support the population PK analysis with sparse sampling data for patients with moderately to severely active CD.

It is planned to enroll approximately 150 *evaluable* patients into a voluntary PK/PD substudy in order to yield sufficient patients per active dose group in the placebo arm of the maintenance study. The data generated by patients in this arm will be used to characterize the etrolizumab/β7 receptor dissociation kinetics. The 150 patient sample size was calculated after considering attrition due to the proportion of non-responders expected to be ineligible for the Maintenance Phase and the 1:1 (etrolizumab: placebo) randomization in the Maintenance Phase further reducing the yield of placebo patients in the maintenance arm *after receiving* etrolizumab induction dose. It is also aimed to include a sufficient number of patients randomized to placebo in the Induction Phase to serve as a parallel control group for the assessment of longitudinal expression of free β7 receptor. This control data will aid in the interpretation of the exposure/occupancy data. The selected sampling timepoints have been chosen to ensure that minimum serum drug concentration (C_{min}), maximum serum drug concentration (C_{max}), and the time course of full to loss of β7 receptor occupancy are captured. In addition, serum samples will be collected in the PK/PD substudy for measurement of β7 receptor ligands, including soluble E-cadherin and MadCAM, in order to assess the pharmacological impact of the etrolizumab/β7 interaction.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

Table 1 contains definitions for the efficacy outcome measures.

3.4.1.1 Co-Primary Efficacy Outcome Measures

Induction Phase

- Clinical remission at Week 14
- Endoscopic improvement at Week 14

Maintenance Phase*, among patients who achieve CDAI-70 response at Week 14*

- Clinical remission at Week 66
- Endoscopic improvement at Week 66

3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for the Induction and Maintenance Phases are listed below.

Induction Phase

- Clinical remission at Week 6
- SES–CD ≤4 (≤2 for ileal patients), with no segment having a subcategory score (i.e., for ulceration size and extent, affected surface, or narrowing) that is >1, at Week 14
- Change in CD signs and symptoms from baseline to Week 14 as assessed by the CD-PRO/SS measure

Maintenance Phase

- Clinical remission at Week 66 among patients who achieved clinical remission at Week 14
- Corticosteroid-free clinical remission at Week 66 *among patients who were receiving corticosteroids at baseline*
- Endoscopic improvement at Week 66 among patients who achieved endoscopic improvement at Week 14
- SES–CD ≤4 (≤2 for ileal patients), with no segment having a subcategory score (i.e., for ulceration size and extent, affected surface, or narrowing) that is >1, at Week 66
- Durable clinical remission
- Corticosteroid-free clinical remission for 24 weeks at Week 66 *among patients who were receiving corticosteroids at baseline*
- Change in CD signs and symptoms from baseline to Week 66 as assessed by the CD-PRO/SS measure

All secondary maintenance outcome measures are among patients who achieve CDAI-70 response at Week 14 unless otherwise stated.

[redacted]

3.4.3 Safety Outcome Measures

The safety outcome measures for this study are:

- Incidence and severity of adverse events
- Incidence of serious adverse events
- Incidence and severity of infection-related adverse events
- Incidence of infection-related serious adverse events
- Incidence and severity of injection-site reactions
- Incidence and severity of hypersensitivity reactions

- Incidence of adverse events leading to study drug discontinuation
- Incidence of specific laboratory abnormalities
- Incidence of malignancies
- Incidence of ATAs to etrolizumab

3.4.4 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are:

- Etrolizumab serum concentrations at *specified timepoints throughout the Induction and Maintenance Phases*

The PK outcome measures for the PK/PD substudy are:

- Observed C_{max} after the first and final doses during the Induction Phase
- Time to C_{max} after the first and final doses during the Induction Phase
- Area under the serum concentration–time curve (AUC) within a dose interval after the first and final doses during the Induction Phase
- Apparent clearance
- Apparent volume of distribution
- Elimination half-life

[redacted]

Table 1 Protocol Definitions

Term	Definition
Crohn's Disease Activity Index score	CDAI score is a composite of eight assessments: number of liquid or soft stools (liquid/soft), abdominal pain, general well-being, presence of complications, taking Lomotil® (diphenoxylate/atropine) or other opiates for diarrhea, presence of an abdominal mass, hematocrit, and percentage deviation from standard weight.
Simple Endoscopic Score for Crohn's Disease	SES-CD is a composite of four assessments, each rated from 0 to 3: size of ulcers, proportion of the surface covered by ulcers, proportion of the surface with any other lesions, and presence of narrowings (stenosis)
Clinical remission	SF mean daily score ≤ 3 and AP mean daily score ≤ 1, with no worsening in either subscore compared to baseline, averaged over the 7 days prior to visit
Endoscopic improvement	A ≥ 50% reduction in the baseline SES–CD score
CDAI-70 response	A decrease from CDAI baseline score of at least 70 points
Disease worsening	During the Induction Phase, the CDAI Week 10 score greater than the patient's baseline (Week 0) score
Clinical relapse	During the Maintenance Phase, clinical relapse is defined as meeting at least one of the following criteria on two consecutive visits (may include unscheduled visits), with at least one of the two consecutive CDAI scores ≥ 220 • CDAI score ≥ the baseline (Week 0) score • CDAI score ≥100 points higher than the Week 14 score

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

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population are refractory or intolerant to CS and/or IS therapy and who have either not received prior anti-TNF therapy (TNF-naive) or who have had prior exposure to one or more anti-TNF therapies (as defined in Section 4.1.1), and who have had an inadequate response, refractory response, or intolerance to CS and/or IS therapy and/or anti-TNFs.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Able and willing to provide written informed consent
- 18–80 years of age at time of consent

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

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

- For men: agreement to remain abstinent or use a condom, as well as not donate sperm during the treatment period and for at least 24 weeks after the last dose of study drug

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

- Diagnosis of CD based on clinical, histopathological, and endoscopic evidence established ≥3 months prior to screening visit.

  The Medical Monitor should be consulted in cases where CD was established at least 6 months prior to screening and a histopathology report is not available. The eligibility of the patient will be considered based on the weight of evidence supporting diagnosis and excluding other potential diagnoses.

- Moderately to severely active disease defined in the Screening Phase by:

  Clinical signs and symptoms resulting in a CDAI score of ≥220 to ≤480 calculated on the day of randomization, requiring a minimum of 4 days of e-diary PRO data from the 7 days prior to randomization **AND**

  A mean daily SF score ≥ 6 **OR** a mean daily SF > 3 and a mean daily AP score > 1 calculated on the day of randomization, requiring a minimum of 4 days of e-diary PRO data from the 7 days prior to randomization (applicable to Cohort 3, the pivotal cohort, only) **AND**

  The presence of active inflammation on screening ileocolonoscopy defined as a SES-CD of ≥7 or ≥4 in cases of isolated ileitis or post-ileocecal resection as determined by the central read model

- Involvement of ileum and/or colon with at least four colonic segments traversable by a pediatric endoscope or three segments (colon and/or ileum) for patients who have undergone a bowel resection for CD

- Meets the following surveillance colonoscopy requirements:

  Surveillance was undertaken at screening or ≤12 months prior in patients with colonic disease for >10 years (regardless of any risk factors for bowel cancer).

  Surveillance was undertaken at screening or ≤ 5 years prior in patients with colonic disease for ≤10 years who have risk factors for bowel cancer.

  (Note—local colonic surveillance guidelines can be followed if patients have no risk factors and colonic disease for ≤ 10 years.)

- Have experienced intolerance, refractory disease, or no response (as defined below) to at least one of the following therapies within 5 years from screening:

  CS Therapy

  Refractory:

  Has signs/symptoms of persistently active disease despite a history of at least one 4-week induction regimen including a dose equivalent to ≥30 mg/day prednisone for 2 weeks if oral or 1 week if IV or ≥9 mg/day oral budesonide

  Intolerance to CS therapy:

  History including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, and infection

  IS Therapy

  Refractory:

  Has signs/symptoms of persistently active disease despite a history of at least one 12-week regimen of oral AZA *(or equivalent)* (≥1.5 mg/kg) or 6-MP *(or equivalent)* (≥0.75 mg/kg) or MTX (≥15 mg/week)

  Intolerance to 6-MP *(or equivalent)*, AZA *(or equivalent)*, or MTX:

  History of intolerance to AZA *(or equivalent)*, 6-MP *(or equivalent)*, and/or MTX (including, but not limited to, infection, nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopenia, and thiopurine methyltransferase genetic polymorphism)

  Anti-TNF Therapy

  Inadequate primary non-response:

  Did not respond (as evidenced by persistent signs/symptoms related to CD after receiving ≥2 induction doses of either infliximab [≥5 mg/kg] or adalimumab [160 mg/80 mg or 80 mg/40 mg] or certolizumab pegol [≥400 mg])

  Inadequate secondary non-response:

  Initially responded to induction therapy with infliximab (≥5 mg/kg) or adalimumab (≥40 mg) or certolizumab pegol (≥400 mg), but experienced signs/symptoms related to recurrence of CD during maintenance

Intolerance:

Experienced a significant injection-site reaction, congestive heart failure, infection, or other condition that precluded continuing use of anti-TNF therapy at any time

Patients who have not previously demonstrated inadequate response or intolerance to one or more anti-TNF therapies are eligible to participate in the study provided they are intolerant or refractory to corticosteroid or immunosuppressant therapy.

4.1.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from study entry.

Exclusion Criteria Related to Gastrointestinal Health

- Has undergone subtotal colectomy with ileorectal anastomosis or has undergone total colectomy
- Short-bowel syndrome
- Has an ileostomy or colostomy
- Has evidence of fixed stenosis or small-bowel stenosis with prestenotic dilation that precludes adequate endoscopic assessment of the bowel
- Diagnosis of UC or indeterminate colitis
- Suspicion of ischaemic colitis, radiation colitis, or microscopic colitis
- Evidence of abdominal or perianal abscess
- Sinus tract with evidence for infection (e.g., purulent discharge) in the clinical judgment of the investigator. Fistulas related to Crohn's disease are not exclusionary.
- Expected to require surgery to manage CD-related complications during the study
- A history or evidence of adenomatous colonic polyps that have not been removed
- Past or present disease-related colonic mucosal dysplasia

Exclusion Criteria Related to Prior or Concomitant Therapy

- Any of the following treatments for CD within 8 weeks prior to randomization:

  Adalimumab

  Certolizumab pegol

  Infliximab
- Any prior treatment with ustekinumab within 14 weeks prior to randomization
- Any prior treatment with etrolizumab or other anti-integrin agents (including vedolizumab, natalizumab, and efalizumab)
- Any prior treatment with anti-adhesion molecules (e.g., anti-MAdCAM-1)

- Prior treatment with T cell– or B cell–depleting agents (e.g., rituximab, alemtuzumab, or visilizumab) within ≤12 months prior to randomization, with the exception of AZA and 6-MP *(or equivalent)*
- Any investigational treatment that included investigational vaccines within 12 weeks prior to randomization in the study or five 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)
- Treatment with corticosteroid enemas/suppositories and/or topical (rectal) 5-aminiosalicylate (5-ASA) preparations ≤2 weeks prior to randomization
- Continued tube feeding, defined formula diets, and/or parenteral alimentation/nutrition as treatment for CD ≥3 weeks prior to randomization
- Expectation of tube feeding, defined formula diets, and/or parenteral alimentation/nutrition as treatment for CD during the study
- Any live or attenuated vaccines ≤4 weeks prior to randomization
- Use of IV steroids during screening, with the exception of a single IV steroid dose administered in the Emergency Department
- Use of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil ≤4 weeks prior to randomization
- Chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs). Prophylactic aspirin use up to 325 mg/day is permitted, as is occasional use of NSAIDs for conditions such as headache, arthritis, myalgia, and menstrual cramps.
- If receiving oral CSs, patients will be excluded unless the dose is stable at ≤20mg/day prednisone or equivalent for ≥2 weeks immediately prior to randomization.
- If receiving ongoing treatment with oral 5-ASA, patients will be excluded if the dose is not stable for ≥2 weeks immediately prior to randomization.
- If receiving ongoing treatment with probiotics (e.g., Culturelle, *Saccharomyces boulardii*) or over-the-counter supplements (e.g., N-acetyl glucosamine, curcumin), patients will be excluded if the dose is not stable for ≥2 weeks immediately prior to randomization.
- If receiving ongoing treatment with ISs (e.g., 6-MP, AZA, or MTX), patients will be excluded if the dose is not stable for ≥8 weeks immediately prior to randomization.
- If receiving ongoing treatment with antibiotics for the treatment of CD, patients will be excluded if the dose is not stable for ≥2 weeks immediately prior to randomization.

Patients may continue to receive ongoing treatment with anti-diarrheals (e.g., loperamide or diphenoxylate with atropine), preferably achieving a stable dose for ≥2 weeks prior to

randomization. However, if the patient and/or the treating physician decides to change the dose or course of anti-diarrheals at any time during screening, these patients will be allowed to participate in study.

Exclusion Criteria Related to Infection Risk

- Congenital or acquired immune deficiency
- Patients must undergo screening for HIV and test negative 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 antiviral treatment and an undetectable HCV RNA at screening or (2) has a known history of HCV antibody positivity with history of undetectable HCV RNA and undetectable HCV RNA at screening in the absence of history of HCV anti-viral treatment
- In the screening hepatitis B assessment (which consists of testing for hepatitis B surface antigen [HBsAg], hepatitis B core anti-body [HBcAb], and if required, hepatitis B virus [HBV] DNA), patients who test positive for HBsAg are excluded from the study. Patients who test positive for HBcAb but negative for HBsAg must have a confirmed negative HBV DNA test result to be eligible for the study and will be required to 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 infection with and/or treatment for *Clostridium difficile* or other intestinal pathogen treatment within 8 weeks prior to randomization.
- A history of active or latent tuberculosis (TB) confirmed by one of the following screening tests:

  Positive tuberculin (purified protein derivative-PPD) skin test

  Or

  Positive QuantiFERON®TB Gold test

  Patients with a documented history of BCG vaccination must have a negative QuantiFERON test result and negative chest radiograph (see below) to be eligible.
- 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 or disseminated viral infections
- Any serious opportunistic infections that occurred ≤ 6 months prior to screening

- Any current or recent signs or symptoms ($\leq$8 weeks before screening) of infection, except for the following:

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

  Fungal infections of the nail beds

  Oral or vaginal candidiasis that has resolved with or without treatment prior to randomization

- Any major episode of infection requiring treatment with IV antibiotics $\leq$8 weeks prior to screening or oral antibiotics $\leq$4 weeks prior to screening. Treatment with antibiotics as adjunctive therapy for CD in the absence of documented infection is not exclusionary.

Exclusion Criteria Related to General Safety

- Pregnancy or lactation
- Lack of peripheral venous access
- Hospitalization (other than for elective reasons) within 4 weeks prior to randomization
- Inability to comply with study protocol, in the opinion of the investigator
- Significant uncontrolled comorbidity such as neurological, cardiac (e.g., moderate to severe heart failure New York Heart Association Class III/IV), pulmonary, renal, hepatic, endocrine, or GI disorders (other than CD)
- Neurological conditions or diseases that may interfere with monitoring for PML
- Clinically significant abnormalities on screening neurologic examination
- History of demyelinating disease
- History of major neurological disorders, including stroke, MS, brain tumor, neurodegenerative disease, or poorly controlled epilepsy
- History of alcohol, drug, or chemical abuse $\leq$6 months prior to screening
- Conditions other than CD that could require treatment with $>$20 mg/day of prednisone (or equivalent) during the course of the study
- History of cancer, including hematologic malignancy, solid tumors, and carcinoma in situ within 5 years before screening

  Non-serious basal cell 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 cervical smear result at any time that indicated the presence of adenocarcinoma in situ (AIS), high-grade squamous intraepithelial lesions (HSIL), or cervical intraepithelial neoplasia (CIN) of Grade $>$1

- History of organ transplant or cell transplantation
- Presence of metal in the body that could a pose hazard during any potential scanning in patients for whom a magnetic resonance imaging (MRI) scan is considered unsafe

Exclusion Criteria Related to Laboratory Values (at Screening)

- Serum creatinine >2 times the upper limit of normal (ULN)
- Impaired hepatic function defined by one of the following:

  Serum transaminases $>3\times$ ULN

  Alkaline phosphatase $>3\times$ ULN

  Total bilirubin $>2.5\times$ ULN (excluding inherited deficiencies such as Gilbert's disease)
- Platelet count $<100{,}000/\mu L$
- Hemoglobin <8 g/dL
- Absolute neutrophil count $<1500/\mu L$
- Absolute lymphocyte count $<500/\mu L$

4.2 METHOD OF TREATMENT ASSIGNMENT, RANDOMIZATION, AND BLINDING

4.2.1 Induction Phase

Following completion of the screening period and after all patient eligibility requirements are confirmed, patients will be randomized to either placebo or etrolizumab low-dose or etrolizumab high-dose (Cohort 1 and Cohort 3) or to etrolizumab low-dose or etrolizumab high-dose (Cohort 2).

The randomization in all cohorts will be stratified by concomitant oral CS treatment (yes vs. no), concomitant IS treatment (yes vs. no), baseline CDAI ≤ 330 (yes vs. no), and TNF−IR patient status (yes vs. no). A permuted blocks randomization method will be used to obtain an approximately 1:2:2 ratio among the placebo, low-dose etrolizumab, and high-dose etrolizumab arms in Cohort 1, an approximately 1:1 ratio between the low-dose etrolizumab and high-dose etrolizumab arms in Cohort 2, and an approximately 2:3:3 ratio among the placebo, low-dose etrolizumab, and high-dose etrolizumab arms in Cohort 3.

During the Induction Phase, the interactive voice or Web-based response system (IxRS) will make etrolizumab low-dose, etrolizumab high-dose, or placebo study treatment kit assignments. To preserve the blind to study drug assignment in the Induction Phase, all patients will receive injections from two separate kits at Weeks 0, 4, 8, and 12. One kit will consist of a 1-mL prefilled syringe with needle safety device (hereafter referred to as PFS) with a 0.7-mL injection volume (delivering placebo or 105 mg of etrolizumab), and one kit will consist of a 2.25-mL PFS with a 1.4-mL injection volume (delivering placebo

or 210 mg of etrolizumab). Depending on dose assignment, one PFS (patients assigned to active drug) or both PFSs (patients assigned to placebo) will contain placebo. At Week 2, all patients will receive a study drug injection from one kit that consists of a 2.25-mL PFS with a 1.4-mL injection volume (delivering placebo or 210 mg of etrolizumab) (see Section 4.3.1). The PFS will contain placebo for patients in the low-dose etrolizumab and placebo arms and active drug for patients in the high-dose etrolizumab arm. The placebo and active drug PFSs are filled and packaged to look identical (other than the difference in volume for the 1-mL PFS vs. the 2.25-mL PFS).

4.2.2 Maintenance Phase

At Week 16, patients treated with etrolizumab who achieved a CDAI-70 response at Week 14 without rescue therapy will undergo a second randomization into the Maintenance Phase in a 1:1 ratio to treatment with placebo or etrolizumab 105 mg SC Q4W *(until n = approximately 480, see Section 3.1.3)*. The randomization will be stratified by CDAI remission at both Weeks 10 and 14 (yes vs. no), induction dose regimen (low dose vs. high dose), concomitant oral CS treatment (yes vs. no), and prior TNF−IR patient (yes vs. no).

Patients who received placebo in either Cohort 1 or 3 and who are eligible for the Maintenance Phase will continue to receive blinded placebo during the Maintenance Phase to keep the blind and avoid any performance bias from the Induction Phase that confounds the Maintenance Phase.

As in the Induction Phase, during the Maintenance Phase, the IxRS will make etrolizumab low-dose/placebo study treatment kit assignments. One treatment kit will be assigned for each visit. Each kit will consist of a 1-mL PFS with 0.7 mL injection volume (delivering placebo or 105 mg of etrolizumab). The placebo and active drug kits are filled and packaged to look identical. Patients performing study drug administration at home may receive two or three kits at a time beginning at Week 16 in order to allow sufficient supply until their next in-clinic visit.

4.2.3 Blinding/Unblinding

Patients, all study site personnel, and the Sponsor and its agents will be blind to treatment assignment throughout the 14-week induction and 52-week maintenance treatment periods of the pivotal studies (i.e., blind to the treatment assignments for induction Cohort 3, and for the maintenance cohort). The IxRS service provider and personnel responsible for performing PK assays (in order to identify appropriate dilutions of PK samples to be analyzed) will be unblinded to patients' randomized treatment assignments. As described in Section 6, treatment assignment will be unblinded to the Sponsor (this does not include representatives of the Sponsor such as Site Monitors) for Cohort 1 at the end of the Induction Phase, or earlier, in the event of an optional interim analysis as described in Section 6.7. However, patients and all study site personnel will remain blinded to individual treatment assignment until after the study is completed (after

all patients have either completed the treatment and safety follow-up period or discontinued early from the study) and the database is locked. Because of the exploratory nature of active-treatment Cohort 2, the Sponsor (including personnel performing PK/PD [redacted] analysis) will not be blinded to dose arm assignments to enable performing [redacted] analyses, if required. These personnel will have no involvement in the Sponsor's oversight of the study conduct. Patients and all study site personnel will remain blinded to individual dose assignment until after the study is completed. The Sponsor, patients, and all study site personnel will remain blinded to individual treatment assignments for patients enrolled in the pivotal Cohort 3.

If unblinding is necessary for patient management, the investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations when knowledge of the study drug assignment is critical to the clinical management of a patient. The Investigator must make reasonable attempts to first discuss the case with the Sponsor's representative Medical Monitor before breaking the treatment code. If the investigator wishes to know the identity of the study drug for any other reason, he or she must contact the Medical Monitor. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding because of a serious adverse event as per Health Authority reporting requirements). The Sponsor Safety Reporting Department (independent from the study team) will break the treatment code for all unexpected serious adverse events (see Section 5.2.2) considered by the investigator to be related to study drug for the purpose of regulatory reporting. The study team will remain blind to study treatment.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Etrolizumab and Placebo

Etrolizumab will be supplied by the Sponsor as a single-use PFS containing 150 mg/mL etrolizumab for SC administration. To preserve the blind to study drug assignment in the Induction Phase, all patients will receive injections from two PFSs at Weeks 0, 4, 8, and 12: a 1-mL PFS with a 0.7-mL injection volume (delivering placebo or 105 mg of etrolizumab) and a 2.25-mL PFS with a 1.4-mL injection volume (delivering placebo or 210 mg of etrolizumab). Depending on dose assignment, one PFS (patients assigned to active drug) or both PFSs (patients assigned to placebo) will contain placebo. At Week 2, all patients will receive a study drug injection from a 2.25-mL PFS with a 1.4-mL injection volume (delivering placebo or 210 mg of etrolizumab). The PFS will contain placebo for patients in the low-dose etrolizumab and placebo arms and active drug for patients in the high-dose etrolizumab arm. In the Maintenance Phase, patients will receive injections from a 1-mL PFS with a 0.7-mL injection volume (delivering placebo or 105 mg of etrolizumab).

Etrolizumab is formulated as 150 mg/mL in 20 mM histidine, 0.2 M arginine succinate, and 0.04% (weight/volume) polysorbate 20, pH 5.8. Each PFS is for single-dose parenteral administration and contains no preservatives.

Drug product composition for the placebo is exactly the same as that of active drug product without the presence of etrolizumab.

Packaging

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

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

Handling

The study drug must be stored according to the details on the product label. The drug label indicates the storage temperature. PFSs of study medication should be refrigerated at 2°C–8°C (35.6°F–46.4°F) and protected from excessive light and heat. PFSs should not be frozen, shaken, or stored at room temperature.

The PFS containing study drug is stable for no longer than 8 hours at room temperature (up to 30°C [86°F]). If a syringe is left at room temperature for longer than this time, it should not be used. In the home setting, patients should be instructed to contact the study site for a replacement.

Used PFS with study drug will be stored at room temperature in designated sharps containers and returned to the site for disposal per local schedule.

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

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

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

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Etrolizumab and Placebo

In the Induction Phase, all patients receive one 0.7-mL injection and one 1.4-mL injection with use of a PFS at Weeks 0, 4, 8, 12 and one 1.4-mL injection at Week 2 (see Appendix 1a). In the Maintenance Phase, all patients will receive one 0.7-mL

injection with use of a PFS Q4W (see Appendix 1b). For the 0.7-mL injection, the device includes a 1-mL long glass syringe with a staked-in stainless steel needle (27G ½'' thin-wall design). For the 1.4-mL injection, the device includes a 2.25 mL glass syringe with a staked-in stainless steel needle (27G ½" thin-wall design). The PFS is a standard design, and the device is fitted with a custom-designed plunger rod and an extended finger flange. A part of the needle cap of the PFS may contain natural rubber latex that may cause allergic reactions in latex-sensitive individuals.

Study site health care professionals (HCPs) will be trained on the use of the PFS and SC administration of study medication into the thigh, abdomen, or upper arm. Patients will in turn be trained in the use of the device by an HCP and an "Instruction for Use" leaflet. In the event that a caregiver will ultimately administer study drug to the patient in the home setting, the caregiver is to be trained. The upper arm site is to be used for caregiver and is not a site to be used for patient self-administration of study treatment.

During the Induction Phase, study medication is to be administered under close supervision of the HCP in a setting where medications and resuscitation facilities are available. The first two treatments (Week 0 [Day 1] and Week 2) will be administered by the HCP and observed by the patient (and/or caregiver). The subsequent treatments in the Induction Phase may be administered by the patient (or caregiver) and observed by the HCP in the clinic setting. Following treatment administrations, 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. Patients with severe hypersensitivity reactions (e.g., stridor, angioedema, life-threatening change in vital signs) must be withdrawn from study treatment. These patients will not be eligible to receive open-label etrolizumab in Part 1 (OLE) of Study GA29145 and are to enter the 12-week safety follow-up in this study, followed by PML monitoring in Part 2 (SM) of Study GA29145.

All adverse events of systemic hypersensitivity reactions or anaphylactoid or anaphylaxis reactions (see Appendix 7) 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).

During the Maintenance Phase, patients will have the option to return to the investigational site or self-administer/have a caregiver administer their treatments at home, upon completion of the training for self-administration and deemed competent by the investigator. Patients and/or the caregiver will be provided with contact information for questions related to self-administration between clinic visits. Competence of the patient or caregiver to administer at home will be documented. Compliance in the home setting is to be monitored with use of an e-diary to record drug administration and return of used and unused medication syringes. Patients and/or the caregiver will be provided with alert cards for themselves and a partner/caregiver, which they shall carry at all

times. These alert cards include guidance on recognizing allergic/anaphylactic/anaphylactoid reactions and how to obtain emergency care in the event such a reaction occurs and information regarding recognition of symptoms of PML.

If the patient cannot administer study medication on the scheduled dosing day, then the patient should administer study medication within a window of ±3 days from the scheduled dosing date, unless a PK blood draw is planned, in which case the dose must be administered within 3 days of the blood draw within 3 days after the visit.

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

The recommended injection sites are the front of the middle thighs and the lower part of the abdomen below the navel except for the 2 inch area directly around the navel. It is recommended that patients be in a comfortable position to self-administer study drug. If a caregiver is administering the injection, the outer area of the upper arm may be used in addition to the abdomen or thigh. If a patient is administering the injection to themselves, they cannot administer the injection in their upper arm. Injections should never be given into areas where the skin is not intact or is tender, bruised, red, or hard. During Weeks 0, 4, 8, and 12 of the Induction Phase when 2 injections are administered (0.7 mL and 1.4 mL), study drug should be injected in two separate injection sites (e.g., middle thigh and lower abdomen). Injecting both doses of study drug in the same area is not recommended. Site personnel will inspect the injection sites at each clinic visit. Record any injection-site reactions, including those following an injection in the home setting (see Section 5.1.1.4), as adverse events.

Guidelines for treatment interruption or discontinuation are provided in Section 4.6.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study, etrolizumab and etrolizumab placebo, are provided by the Sponsor. The study site will acknowledge receipt of IMPs with use of 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 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 Assessment of Compliance

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

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

Patients will return all unused PFSs in the provided boxes at each visit as a measure of drug accountability and patient compliance. Site personnel will monitor the medication records from the e-diary via an online portal.

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

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

Any unused study drug and Drug Return Records should be returned to the Monitors, unless alternate destruction has been authorized by the Sponsor or required by local or institutional regulations (Section 4.3.3). The investigator's copy of the Drug Return Record(s) must accurately document the return of all study drug supplies to Sponsor.

4.3.5 Destruction of the Investigational Medicinal Product/Comparator

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

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

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

4.3.6 Reporting of Prefilled Syringe Complaints/Events

For reporting of PFS complaints or events, see Section 5.3.4.

4.3.7 Post-Trial Access to Etrolizumab

For post-trial access to etrolizumab, see Section 4.5.9.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening to the study completion/early withdrawal visit.

Anti-diarrheal medications are permitted if used to manage chronic diarrhea, but every attempt should be made to keep the dose/regimen stable. Any changes in the dose/regimen after baseline (Week 0) must be captured by the investigator and/or patient.

Occasional use of NSAIDs or acetaminophen is permitted for pain relief (e.g., in the case of headache, arthritis, myalgia, etc.). Prophylactic aspirin use up to 325 mg/day is also permitted.

All medications used must be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Management of Concomitant Crohn's Disease Medication in the Induction Phase

During the Induction Phase, in all cohorts, concomitant CSs will be maintained at a stable dose of ≤20 mg/day prednisone or equivalent or ≤6 mg/day oral budesonide.

4.4.2 Management of Immunosuppressants throughout the Study

Patients must remain on stable doses of ISs (e.g., AZA *(or equivalent)*, 6-MP *(or equivalent)*, MTX) throughout the study unless dose reduction or discontinuation is required because of a toxicity related to the medication. Generally accepted criteria for discontinuation of IS due to toxicity include, but are not limited to, acute pancreatitis, severe leukopenia, severe thrombocytopenia, or significant elevations of the liver-associated enzymes from baseline, especially in the presence of an elevated total bilirubin. The ultimate decision to discontinue IS remains at the discretion of the Investigator.

4.4.3 Management of Concomitant Crohn's Disease Medication in the Maintenance Phase

The CS dose should be tapered starting at Week 14 according to the following schedule:

- ≤20 mg/day prednisone (or equivalent): titrated via dose reduction of 2.5 mg/week until discontinuation
- ≤6 mg/day oral budesonide: titrated via dose reduction of 3 mg every 2 weeks until discontinuation

For patients who cannot tolerate the dose tapering without recurrence of clinical symptoms, the CS dose may be increased but should not exceed the baseline dose (i.e., dose at Week 0 of the study), and the dose-tapering regimen should be re-initiated within 2 weeks.

Patients taking concomitant IS therapy (AZA *(or equivalent)*, 6-MP *(or equivalent)*, or MTX) must remain on stable doses throughout the study unless dose reduction or discontinuation is required because of a toxicity related to the medication.

4.4.4 Permitted Rescue Therapy

4.4.4.1 Rescue Therapy in the Induction Phase

This is defined as medication prescribed for new or worsening CD symptoms and includes:

- Any new CS or IS therapy for CD
- Any increase in dose or regimen of baseline Crohn's medications

Antibiotics, 5-ASAs, anti-diarrheals, probiotics, herbal/ayurvedic, nutritional and homeopathic supplements are not considered as rescue therapies.

Patients requiring rescue therapy during the Induction Phase will be considered non-responders for the primary analysis and will not be eligible for the Maintenance Phase.

4.4.4.2 Rescue Therapy in the Maintenance Phase

This is defined as medication prescribed for new or worsening CD symptoms and includes:

- Any new CS or IS therapy for CD
- Increase in dose of IS therapy above the baseline (Week 0) dose
- Increase in the dose of CS therapy above a patient's baseline (Week 0) dose (applicable to patients requiring CS at baseline)

Antibiotics, 5-ASAs, anti-diarrheals, probiotics, herbal/ayurvedic, nutritional, and homeopathic supplements are not considered as rescue therapies.

4.4.5 Prohibited Therapy

Patients should not be treated for continuing signs and symptoms of CD with any medication that is prohibited to be taken concomitantly with etrolizumab; these include, but are not limited to, anti-integrins, anti-adhesion molecules (e.g., anti-MAdCAM-1), T- or B-cell–depleting agents with the exception of 6-MP and AZA *(or equivalent)*, TNF antagonists, *antagonists of IL-23 ±IL-12 (e.g., ustekinumab)*, anti-metabolites, cyclosporine, and tacrolimus. Any patient treated with a prohibited medication in the Induction or Maintenance Phase will be considered a non-responder for the purpose of the primary analysis. These patients must be immediately discontinued from etrolizumab; they will not be eligible for Part 1 (OLE) of Study GA29145 and must enter the 12-week safety follow-up period. They will then be asked to enroll in an extended PML-monitoring phase (Part 2 [SM] of Study GA29145) for 92 weeks.

CS enemas/suppositories and/or topical (rectal) 5-ASA preparations are also prohibited medications. Patients taking these medications will be considered non-responders for the purpose of any endoscopic analyses. These treatments must be discontinued, but patients may continue to receive etrolizumab and may still be eligible for Part 1 (OLE) of Study GA29145.

4.5 STUDY ASSESSMENTS

The description of the study assessments for the Screening, Induction, and Maintenance Phases are described in Sections 4.5.2, and 4.5.3 and the Schedule of Assessments is provided in Appendix 1a and Appendix 1b.

4.5.1 Informed Consent Forms and Screening Log

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

A separate informed consent is required for patients participating in the optional PK/PD substudy.

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

The screening period should not exceed 35 calendar days.

All screening tests and evaluations (see Appendix 1a for screening tests and evaluations and Section 4.5.7 for description of test and evaluations) will be performed within 35 days prior to Day 1 except for the ileocolonoscopy, which should be performed during the screening and at least 9 days prior to the date of randomization (see Section 4.5.7.6). Laboratory samples should be collected from the patient early in the screening period to allow time for the laboratory results to be available for review by the site for eligibility. The ECG and chest X-ray can be obtained any time before Day 1 (see Section 4.5.7.9 and Section 4.5.7.15). All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before Day 1. The investigator will maintain a screening log to record details of all patients screened as described in Section 4.5.1.

4.5.2.1 Re-Screening

If a patient does not meet all the eligibility criteria within 35 days after the original screening visit, re-screening is permitted. Patients found to be ineligible for entry into the study may be re-screened only once (e.g., if the patient develops additional manifestations of 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 re-screening occurs.

Re-screening 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 re-screening randomization visit.

- HIV preliminary and confirmatory tests
- Hepatitis C virus (HCV) antibody test
- Hepatitis B assessment (i.e., surface antigen [HBsAg] core anti-body [HBcAb], and if required, hepatitis B virus [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 re-screened with the above tests.

Patients who are classified as screen failures due to the presence of *C. difficile* may be re-screened 60 days after the end of successful treatment. Full re-screening will be required.

As described in Section 4.5.7.14, if a negative TB screening test result has been documented within 3 months before screening, or re-screen, no new test is needed.

Patients who met the SES–CD eligibility criterion during their first screen do not need to repeat the ileocolonoscopy procedures as long as date of the ileocolonoscopy during the initial screening assessment was ≤ 4 weeks prior to the scheduled randomization visit after re-screen.

Patients who have been hospitalized (other than elective reasons) ≤5 weeks prior to the scheduled randomization visit after re-screen are not eligible for the study.

4.5.3 Study Assessments during Induction and Maintenance

Visits for the Induction and Maintenance Phases should occur within ±3 days of the specified time, except for CD assessment visits at Weeks 10, 14, 66, and early withdrawal (i.e., visits not associated with study drug administration), which may occur within ±7 days of the specified time.

During the Induction Phase, all visits take place in the clinic; however, in the Maintenance Phase, patients are contacted by telephone (a telephone visit) for the purpose of study assessment rather than making a clinic visit for prespecified visits (indicated in Appendix 1a and Appendix 1b). Blood draws for the PK/PD substudy may be collected by appropriately qualified personnel in the patient's home or other suitable location away from the clinic. If samples are not collected at the clinic, samples will be sent on the day of collection to a central laboratory for storage until analysis begins.

All assessments are performed on the day of the specified visit, except where a time window is specified. Assessments scheduled on the day of study drug administration (e.g., blood draws, pregnancy tests) should be performed prior to dosing, unless otherwise noted.

When study drug administration in the home (or the clinic, if applicable) is required on the same day as clinic assessments, drug is to be administered at home after the clinic visit.

4.5.4 Assessments at Study Completion

Patients who complete the treatment phase will be asked to visit the clinic for Week 66 assessments. The end of study treatment (Week 66 or the early withdrawal from treatment visit) is followed by a 12-week Safety Follow-Up Phase (telephone visit at Week 6 and clinic visit at Week 12; see Appendix 1a, Appendix 1b, and Appendix 2). Patients who are eligible and consent to receive open-label etrolizumab will enroll directly into Part 1 (OLE) of Study GA29145 after the Week 66 visit is completed; these patients will not enter the 12-week Safety Follow-Up Phase of the study. Ineligible patients or those who choose not to enroll in Part 1 (OLE) of Study GA29145 will be asked to enroll in Part 2 (SM) of Study GA29145 for extended PML follow-up after completion of the 12-week Safety Follow-Up Phase of the study.

4.5.5 Early Withdrawal from Study

It is critical to the integrity of this study that patients adhere to the visit schedule outlined in the protocol. As such, every reasonable effort should be made to convey to the patients the importance of remaining on the study. All patients withdrawing from the study prior to Week 66 should complete an early withdrawal visit, including those patients who are enrolling in Part 1 (OLE) of Study GA29145 at the end of the Induction Phase or prior to completion of the Maintenance Phase. Assessments are specified in the Schedule of Assessments in Appendix 1a and Appendix 1b.

The early withdrawal visit should take place 4 weeks (±7 days) after the last dose of study drug. Patients who wish to withdraw from the study during the Safety Follow-Up Phase should also complete an early withdrawal visit.

4.5.6 Assessments at Unscheduled Visits

An unscheduled visit may occur at any time during the study (i.e., because of relapse of disease or an adverse event). Patients who are seen by the investigator or site staff at a time point not required by the protocol should undergo symptom-driven assessments (e.g., undergo a PML assessment interview and neurological examination only if patient reports symptoms suspected of PML).

See Appendix 1a and Appendix 1b for assessments that if performed in case of an unscheduled visit should be recorded on the eCRF.

4.5.7 Description of Visit Activities

4.5.7.1 Medical History 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). A detailed history of medication used for CD is required for the 5 years prior to screening.

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

4.5.7.2 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 and the PML Objective Checklist by the investigator (see Section 4.5.7.8 for PML assessment details and Appendix 6 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 at Weeks 14, 24, 32, 44, 56, and 66 (or Early Withdrawal Visit). New or worsened abnormalities from screening should be recorded as adverse events, if appropriate.

[redacted]

[redacted]

[redacted]

4.5.7.4 Vital Signs, Height, and Weight

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 at screening and at Weeks 0, 4, 8, 12, 16, 24, 32, 44, 56, and 66 (or Early Withdrawal Visit). Record vital signs before study drug administration at clinic visits only.

Height should be measured at screening only.

Weight should be measured during screening and at Weeks 0, 10, 14, 24, 28, 32, 44, 56, and 66 (or Early Withdrawal Visit).

4.5.7.5 Crohn's Disease Activity Assessments

Collect a detailed history of CD, including date of diagnosis, disease severity, hospitalizations, and extraintestinal manifestations at screening.

Disease severity will be evaluated using the CDAI, SF, AP, and SES–CD. The CDAI, SF, and AP are described in Appendix 9. The SES–CD is assessed through endoscopy and is a composite of four factors (ulcer size, percentage of ulcerated surface, percentage of surface affected by other lesions, and extent of stenosis) in up to five ileocolonic segments.

The CDAI, SF, and AP scores will be calculated at Weeks 0, 10, 14, 24, 28, 32, 44, 56, and 66 (or Early Withdrawal Visit). SES–CD assessments will take place at screening and Weeks 14 and 66 (or Early Withdrawal Visit).

Abdominal pain will be additionally assessed throughout the study with the Abdominal Pain Questionnaire (APQ) recorded daily on an e-diary (see Appendix 11).

For the Week 14 and 66 visits, the ileocolonoscopy should be scheduled on the day of the visit. If this is not possible, the ileocolonoscopy should be performed no later than 5 days after the visit.

4.5.7.6 Ileocolonoscopy with Biopsies

The ileocolonoscopy will be performed within the screening period and at least 9 days prior to randomization and at Weeks 14 and 66 and/or withdrawal from study (Early Withdrawal visit; see Appendix 1a and Appendix 1b).

Patients are to prepare their bowel prior to the ileocolonoscopy procedures. Medications used for bowel preparation should be reported on the concomitant medications pages of eCRF.

[redacted].

A full colonoscopy is required to guard against enrolling patients with colonic carcinoma and dysplasia. Depending on a patient's risk factor for bowel cancer and their last surveillance colonoscopy, the surveillance can be done in combination with this screening ileocolonoscopy. Refer to Section 4.1.1 regarding surveillance colonoscopy requirements for inclusion into this study.

For each patient, a video recording the entire ileocolonoscopy procedure is performed using a recording device issued or recommended by the central read vendor. All video recordings will be edited by the central read vendor to produce video clips that are representative of each segment of the colon visualized up to the terminal ileum. The video clips will be read centrally for mucosal lesions and endoscopic severity by an independent gastroenterologist experienced in IBD who is blind to the patient's clinical activity and treatment allocation. When scoring the SES–CD, please use the worst affected portion of each segment.

In all cases, video recordings should be performed prior to biopsy. Technical instructions for making the video recording will be provided separately (these instructions will include how to capture the depth of insertion and how to mark bowel segments during the recording).

Each patient entered into the study will have biopsy sample collections performed during the ileocolonoscopy at Screening, Week 14, and Week 66 as follows:

At Screening: a total of 9 pairs (18 biopsy samples)

- Two pairs of biopsies (4 biopsy samples) taken from an area that is within 20–40 cm from the anal verge (sigmoid colon) and one pair of biopsies (2 biopsy samples) should be taken from the transverse colon. The three pairs of biopsies should be placed in formalin at the sites.
  - If the colon segment is normal, random biopsies should be obtained and labeled as "non-inflamed" along with the location (i.e., transverse colon, sigmoid colon) on the central laboratory requisition form.
  - If the colon segment has macroscopic disease but no discrete lesion (e.g., ulcers), the biopsies should be taken from the most severely affected area and labeled as "inflamed" along with the location (i.e., transverse colon, sigmoid colon) on the central laboratory requisition form.
  - If the colon segment has discrete lesion (e.g., ulcers), the biopsies should be taken perpendicular to the edge of the largest lesion present and labeled as "inflamed" along with the location (i.e., transverse colon, sigmoid colon) on the central laboratory requisition form. Obtaining biopsies from the base of the ulcer should be avoided.
- Six pairs of biopsies (12 biopsy samples) preferentially from the inflamed terminal ileum or if necessary the inflamed ileocecal valve or another more distal inflamed region of the colon.
  - Patients with active disease of the terminal ileum (Montreal location category L1 or L3; Silverberg et al. 2005) will have biopsies taken of inflamed mucosa from this region if it is accessible during endoscopy. These biopsy samples will be identified as ileum samples.
    - Four pairs of biopsies (8 biopsy samples) should be placed in formalin at the sites.
    - Each of the remaining two pairs of biopsies (4 biopsy samples) should be placed in separate stabilization buffer (RNAlater) and shipped to a central laboratory for storage at –80°C.
  - If the terminal ileum is not accessible in patients with L1 or L3 disease, the biopsies will be taken either from an inflamed region of the ileocecal valve or another more distal inflamed region of colon. These biopsy samples will be identified as colonic samples.
    - Four pairs of biopsies (8 biopsy samples) should be placed in formalin at the sites.
    - Each of the remaining two pairs of biopsies (4 biopsy samples) should be placed in separate stabilization buffer (RNAlater; one pair per tube) and shipped to a central laboratory for storage at –80°C.

At Weeks 14 and 66 (or Early Withdrawal Visit): a total of 6 pairs (12 biopsy samples) at each timepoint

- Two pairs of biopsies (4 biopsy samples) taken from an area that is within 20-40 cm from the anal verge (sigmoid colon) and one pair of biopsies (2 biopsy samples) should be taken from the transverse colon. The three pairs of biopsies should be placed in formalin at the sites.
  - If the colon segment is normal, random biopsies should be obtained and labeled as "non-inflamed" along with the location (i.e. transverse colon, sigmoid colon) on the central laboratory requisition form.
  - If the colon segment has macroscopic disease but no discrete lesion (e.g., ulcers), the biopsies should be taken from the most severely affected area and labeled as "inflamed" along with the location (i.e. transverse colon, sigmoid colon) on the central laboratory requisition form.
  - If the colon segment has discrete lesion (e.g., ulcers), the biopsies should be taken perpendicular to the edge of the largest lesion present and labeled as "inflamed" along with the location (i.e. transverse colon, sigmoid colon) on the central laboratory requisition form. Obtaining biopsies from the base of the ulcer should be avoided.
- Three pairs of biopsies (6 biopsy samples) preferentially from the inflamed terminal ileum or if necessary the inflamed ileocecal valve or another more distal inflamed region of the colon.
  - Patients with active disease of the terminal ileum (Montreal location category L1 or L3; Silverberg et al. 2005) will have biopsies taken of inflamed mucosa from this region if it is accessible during endoscopy. These biopsy samples will be identified as ileum samples.
    - Two pairs of biopsies (4 biopsy samples) should be placed in formalin at the sites.
    - One pair of biopsies (2 biopsy samples) should be placed in a stabilization buffer (RNAlater) and shipped to a central laboratory for storage at −80°C.
  - If the terminal ileum is not accessible in patients with L1 or L3 disease, the biopsies will be taken either from an inflamed region of the ileocecal valve or another more distal inflamed region of colon. These biopsy samples will be identified as colonic samples.
    - Two pairs of biopsies (4 biopsy samples) should be placed in formalin at the sites.
    - One pair of biopsies (2 biopsy samples) should be placed in a stabilization buffer (RNAlater) and shipped to a central laboratory for storage at −80°C.

[redacted] Samples will be sent to the central laboratory to be paraffin embedded and for further storage or distribution (unless analysis is to be performed locally, as indicated).

4.5.7.7 Neurological Examination

A neurological examination including assessments of cranial nerves, motor and sensory function, coordination, and mental status will be performed by a qualified HCP (e.g., investigator, physician assistant, nurse, nurse practitioner; a neurology consultation is not required) prior to any other assessment during screening and at Weeks 4, 14, 24, 32, 44, 56, and 66 (or Early Withdrawal Visit).

Clinically significant findings from the neurological examination should be recorded as medical history during screening, and new clinically significant findings should be recorded as adverse events after the first dose of study drug.

4.5.7.8 Progressive Multifocal Leukoencephalopathy Assessment

Study site personnel and patients will be educated regarding the signs and symptoms of PML.

Patients will be closely monitored during the course of the study for any new symptoms or signs suggestive of PML through regular neurological examinations and administration of the PML Subjective Checklist (symptom assessment; see Appendix 5) and the PML Objective Checklist (neurologic evaluation; see Appendix 5). The PML assessment should be performed prior to any other assessment along with the neurological examination (see Section 4.5.7.7) by a qualified HCP (e.g., investigator, physician assistant, nurse, nurse practitioner; a neurology consultation is not required) during in-clinic visits at screening and at Weeks 4, 14, 24, 32, 44, 56, and 66 (or Early Withdrawal Visit).

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.

If a patient has a positive finding on the PML Subjective Checklist that is accompanied by a positive finding on the PML Objective Checklist or if there is a strong clinical suspicion for PML, the event should be reported expeditiously as an adverse event of special interest within 24 hours (see Section 5.2.1 and Appendix 6 for the Algorithm for Evaluation of PML). If PML is suspected, dosing with study treatment for that patient should be suspended and the patient should be promptly referred to a neurologist to rule

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

Dosing with study treatments can be resumed only if PML has been ruled out (see Appendix 6 for the Algorithm for Evaluation of PML).

After completing the Maintenance Phase, patients not enrolling in Part 1 (OLE) of Study GA29145 to receive treatment with open-label etrolizumab will enter the 12-week Safety Follow-Up Phase (see Appendix 2). The PML assessment interview and neurologic examination are to be performed at Week 12 of the safety follow-up.

Following the 12-week safety follow-up, all patients will be requested to continue monitoring for PML for an additional 92 weeks by enrolling in Part 2 (SM) of Study GA29145, giving a total of 2 years PML follow-up after the last dose of study medication. No study drug will be administered to patients during Part 2 (SM).

4.5.7.9 Electrocardiograms

ECGs will be performed during screening or prior to randomization at Week 0, Week 16, and Week 66 (or Early Withdrawal Visit).

A 12-lead ECG with formal readings should be obtained for each patient from the same machine whenever possible. To minimize variability, it is important patients be in a resting position for ≥10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be obtained prior to any scheduled vital sign measurements and blood draws.

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

4.5.7.10 Patient-Reported Outcomes

PROs ([redacted], APQ and the loose stool frequency, abdominal pain, and general well-being components of the CDAI) will be collected to help characterize the patient-reported clinical profile of etrolizumab. The instruments will be translated as required into the local language.

PRO data are collected electronically with the use of electronic PRO (ePRO) devices (i.e., e-diary and tablet). The investigator staff will provide the patient with an e-diary

and instructions for completing the PRO questionnaires electronically for those PROs that need to be completed outside of the clinic. Patients will also be instructed to contact the site promptly if they have any questions about the use of the e-diary during screening or at any time during the study. For instances when PROs are to be completed at the clinic, the patient will fill them out on a tablet.

Review electronic data captured by the patient since the previous study visit with the patient at each clinic visit. ePRO data is collected and assessed at visits as outlined below and noted in the Schedule of Assessments (see Appendix 1a and Appendix 1b).

During screening, patients will be instructed on how to appropriately use and complete questions on the e-diary. The signs and symptoms of CD, specifically, number of liquid or soft stools, abdominal pain, and general well-being, must be recorded daily throughout the study, including the screening period.

To ensure instrument validity and that data standards meet Health Authority requirements, the PROs completed at the sites ([redacted]) must be administered at the investigational site prior to the completion of other non-PRO assessments and before the patient receives any disease-status information or study drug during that visit.

Crohn's Disease Activity Index

The CDAI quantifies the signs and symptoms of patients with CD (see Appendix 9). The CDAI consists of eight factors; each factor is summed after adjustment with a weighting factor (Best et al. 1979). The components of the CDAI include number of liquid or soft stools, abdominal pain, general well-being, presence of complications, use of Lomotil® (diphenoxylate/atropine) or other opiates for diarrhea, presence of an abdominal mass, hematocrit, and percentage deviation from standard weight. Of the eight factors of the CDAI, three are patient reported (number of liquid or soft stools, abdominal pain, and general well-being), four are based on physician assessment (presence of complications, use of Lomotil® or other opiates for diarrhea, presence of abdominal mass, and percentage of deviation from standard weight, which is based on the patient's weight at the visit), and one factor is based on a blood test (hematocrit). Patients are to report their abdominal pain severity, loose-stool frequency, and general well-being on the e-diary on a daily basis. The weighted sum of the average scores over 7 days is calculated for the PRO component of the CDAI score. The Bristol Stool Scale is provided to patients as a reference for determining loose stools (Types 6 and 7 on the Bristol Stool Scale; see Appendix 8). Because the ileocolonoscopy preparations can interfere with the assessment of other clinical parameters, e-diary entries used to calculate the complete CDAI should not correspond to day(s) of bowel preparation, endoscopy, or the day after endoscopy.

Stool Frequency and Abdominal Pain

Two patient reported factors will be evaluated: the frequency of liquid or soft stools and abdominal pain. The score is calculated using the unweighted mean number of

liquid/very soft stools and mean AP (on a 0–3 scale) for the 7 days prior to the assessment visit. Patients are to report their loose-stool frequency (the Bristol Stool Scale will be provided) and abdominal pain severity on the e-diary on a daily basis. As with the CDAI, the SF and AP scores should not use e-diary entries that correspond to day(s) of bowel preparation, endoscopy, or the day after endoscopy, to avoid interference related with the ileocolonoscopy.

Abdominal Pain Questionnaire

The 0-10 point Abdominal Pain Questionnaire (APQ) is an 11-point numeric rating scale to assess the worst abdominal pain on a daily basis (see Appendix 11). A higher score indicates a greater severity of abdominal pain. The APQ has a recall specification of 24 hours. As with the CDAI, SF, and AP scores, the calculated APQ score should not use e-diary entries that correspond to day(s) of bowel preparation, endoscopy, or the day after endoscopy, to avoid interference related with the ileocolonoscopy.

[redacted]

4.5.7.11 Study Drug and Compliance

During the Induction Phase, patients will receive placebo, low-dose etrolizumab, or high-dose etrolizumab at Weeks 0, 2, 4, 8, and 12.

During the Maintenance Phase, patients will receive placebo or low-dose etrolizumab at Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, and 64. After completing Week 16, patients have the option to return to the investigational site or to self-administer/have a caregiver administer their subsequent doses at home within ±3 days of their scheduled dose unless a PK blood draw is planned (see Appendix 1b and Appendix 3), in which case the dose must be administered after the blood draw on the day of visit or within 3 days after the visit.

If the patient chooses to administer drug at home during the Maintenance Phase, the patient is to record the location of each injection and whether the injection was successfully administered following each home dose administration.

4.5.7.12 Concomitant Medications

Concomitant medications are monitored beginning at the Screening Phase and reviewed at each study visit, including any unscheduled visit(s).

4.5.7.13 Adverse Events

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsy sample collection, discontinuation of medications) should be reported. All adverse events will be monitored beginning at Week 0 and will be reviewed at each study visit including any unscheduled visit(s). See Section 5.2.1 for more details about adverse events and safety reporting.

4.5.7.14 Tuberculosis Screening

Patients will be evaluated for TB at screening. The PPD skin test and QuantiFERON®-TB Gold are acceptable screening assays for latent *Mycobacterium* TB infection.

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

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

Patients with a history of bacille Calmette-Guérin vaccination should be screened only with use of the QuantiFERON®-TB Gold test.

An indeterminate QuantiFERON®-TB Gold test should either be repeated or followed up with a PPD tuberculin skin test in patients who are eligible to have a PPD tuberculin skin test performed.

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

  Positive QuantiFERON®-TB Gold test

  Two successive indeterminate QuantiFERON®-TB Gold tests

  Positive PPD tuberculin skin test

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

  Negative QuantiFERON®-TB Gold test

  Negative PPD tuberculin skin test

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

4.5.7.15 Chest X-ray

A chest X-ray will be conducted at screening and used to detect TB. 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.

4.5.7.16 Pregnancy Testing

All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening.

Urine pregnancy tests are performed at Weeks 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, and 64 (or Early Withdrawal visit). A urine pregnancy test is also performed at Week 12 (or Early Withdrawal visit) of the 12-Week Safety Follow-up Phase. During the period where telephone visits are conducted, patients can take a urine pregnancy test at home and report the test result via e-diary.

For a positive urine pregnancy test result, confirm by a serum pregnancy test.

4.5.7.17 Laboratory Assessments

Laboratory assessments are performed at Screening, Induction, and Maintenance as indicated on the Schedule of Assessments (see Appendix 1a and Appendix 1b and described below).

Guidelines for Laboratory Assessments

General Guidelines:

- All laboratory investigations will be sent to one or more central laboratories for analysis.
- Laboratory sample handling and shipment are outlined in the Study Manual.

Screening Phase Guidelines

- All patient laboratory samples required for screening should be collected early in the screening period to allow time for laboratory results to be available for review by the site for eligibility.
- Patients may be re-screened for laboratory inclusion and exclusion criteria up to two times, with the exception of *C. difficile* infection. Patients who are classified as screen failures because of the presence of *C. difficile* infection may be re-screened 60 days after successful treatment. For all other laboratory inclusion and exclusion criteria, if a patient fails to meet the criteria a third time, he or she becomes a screen failure.
- Laboratory testing repeated because of administrative or technical issues (e.g., breakage of a sample vial during transit to the central laboratory or degradation of a sample during transportation) is not considered re-screening.
- Laboratory samples should be drawn prior to the initiation of bowel preparation.
- Test results that are borderline or indeterminate may be repeated within the Screening Phase.

Induction and Maintenance Phase Guidelines

- On days of study drug administration, take laboratory samples before the administration of study drug.

Laboratory assessments include the following:

Hematology and Clinical Chemistry

- 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)

    Collected during screening and at Weeks 0, 10 (hematocrit only), 14, 24, 28 (hematocrit only), 32 (hematocrit only), 44, 56 (hematocrit only), and 66 (or Early Withdrawal visit)

- Serum chemistries including liver function test (sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatine phosphokinase, and uric acid)

  Collected during screening and at Weeks 0, 14, 24, 44, and 66 (or Early Withdrawal visit)

- [redacted]

- HIV, hepatitis B, and hepatitis C

  Collected during screening only

  Patients who are HBV antibody positive should have HBV DNA measured at Weeks 14, 24, 32, 44, 56, and 66.

- 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.

[redacted]

Anti-Therapeutic Antibody Assessments

- Anti-therapeutic antibody (ATA) serum samples will be collected for the detection and characterization of antibodies against etrolizumab in all patients. Samples are analyzed using validated assays. For ATA samples without matched PK determinations, etrolizumab concentrations may be measured for the purpose of helping interpret ATA data. [redacted]. ATA samples are to be collected before dosing at Weeks 0, 4, 14, 24, 32, 44, 66 (or Early Withdrawal visit), and unscheduled visit.

Population Pharmacokinetic Assessments

- PK serum samples will be collected for determination of etrolizumab concentrations and are to be analyzed using a validated assay. PK serum samples are to be collected before dosing *(if specified sample collection timepoint is a dosing date)* at Weeks 0, 10, 14, 16, 24, 28, 32, 44, and 66 (or Early Withdrawal visit).

Optional Whole-Blood DNA

- Whole-blood DNA may be collected and processed for genetic analysis from consenting patients at randomization. These samples may be assayed for mRNA expression, genetic variation, and other biomarker(s) to predict response or toxicity to etrolizumab.

Optional PK/PD Substudy Assessments

- The following samples will be collected only from all patients consenting to participate in the PK/PD substudy (see Appendix 3 for additional substudy sampling schedule) in addition to the PK/PD samples collected from all patients in the main study.

  Receptor Occupancy: Whole-blood samples will be collected during screening, Day 1 before dosing, Days 3, 4, or 5 (only one of these days), and at Weeks 4, 10, 14, 16, 20, 24, 28 (all predose)

  PK serum samples will be collected on Days 3, 4, or 5 (only one of these days), Weeks 2, 4, 12 (all predose), Days 3, 4, or 5 post Week 12 dose (only one of these days), and predose on Week 20 (or Early Withdrawal visit).

  Substudy PD serum samples will be collected at Days 3, 4, or 5 (only one of these days) and at predose on Weeks 2, 4, and 20 (or Early Withdrawal visit).

Urinalysis

- Collected during screening and at Week 0 (before the first dose of study drug)

Stool Samples

- [redacted]
- Collected during screening and at Weeks 14, 66, and early withdrawal prior to the prep for the ileocolonoscopy
- [redacted]

Biopsies

- Collected during screening and at Weeks 14 and 66 (see Section 4.5.7.6)

4.5.7.18 Samples for Roche Clinical Repository

Overview of the Roche Clinical Repository

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

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. In addition, any residual biopsy and blood samples for biomarkers left over at the end of the study and analyses will be transferred to the RCR for consenting patients. RCR specimens are used to achieve the following objectives:

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

Approval by the Institutional Review Board or Ethics Committee

Sampling for the RCR is contingent upon the review and approval of the [redacted] research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol will not be applicable at that site.

Sample Collection

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

Samples obtained [redacted] but not utilized or not entirely consumed are to be transferred to the RCR.

Specimen types include:

- [redacted]
- [redacted]
- Ileum/Colon biopsy samples (formalin and stabilization buffer [such as RNAlater or a similar buffer]; see for specific collection timepoints)
- Stool samples

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

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

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

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

Confidentiality

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

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

Patient medical information associated with RCR specimens is confidential and may 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.

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

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

Consent to Participate in the Roche Clinical Repository

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

The investigator should document whether the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

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

Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes with use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GA29144 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study GA29144.

Monitoring and Oversight

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

4.5.8 Safety Follow-Up Assessments

Safety follow-up is conducted in this study for a period of 12 weeks after the last dose of study drug for patients not enrolling in Part 1 (OLE) of Study GA29145 (see Appendix 2). Patients are assessed at 6-week intervals during this period, one assessment by phone and one in-person clinic visit. The visits should be scheduled on the basis of the date of the last dose of study drug (i.e., the Week 6 telephone visit should take place 6 weeks after the last dose of study drug and the Week 12 in-person clinic visit should take place 12 weeks after the last dose of study drug). Adverse events should be followed as outlined in Section 5.3.

Following the 12-week safety monitoring period, patients will be asked to enroll in Part 2 (SM) of Study GA29145, where they are monitored for PML for an additional 92 weeks. Patients enrolling in Part 2 (SM) for the extended PML monitoring will NOT receive treatment with open-label etrolizumab. During the extended PML follow-up period in Part 2 (SM), patients will have telephone visits every 6 months to assess for any 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 will be asked to return to the clinic within 4 weeks (±3 days) after the last dose of study drug or last scheduled visit for an early withdrawal visit (see Appendix 2).

See for the Schedule of Assessments performed at the study completion/early withdrawal from treatment visit.

After the study completion, adverse events should be followed as outlined in Sections 5.4 and 5.5. See Appendix 2 for the schedule of 12-week safety follow-up assessments.

4.5.9 Eligibility for Entry to Open-Label Extension-Safety Monitoring Study

The OLE-SM study will be conducted under a separate protocol (Study GA29145), and eligible patients as described below must be willing and able to provide separate informed consent to enter this study.

Note: Patients who are ineligible or who do not wish to receive open-label etrolizumab (Part 1 [OLE] of Study GA29145) are asked to enroll in the 92-week extended PML monitoring phase (Part 2 [SM] of Study GA29145) after completing the 12-week safety follow-up in this study.

4.5.9.1 Inclusion Criteria for Part 1 (OLE) of Study GA29145

The following patients may be eligible to enroll in Part 1 (OLE) of Study GA29145 between and including Weeks 10 and 14

- Patients who experienced disease worsening, defined as a CDAI Week 10 score greater than the patient's baseline (Week 0) score.

The following patients may be eligible to enroll in Part 1 (OLE) of Study GA29145 at Week 14 (but see exclusion criteria in Section 4.5.9.2)

- Patients who are not eligible for the Maintenance Phase
- *Patients who complete the Week 14 visit after the Maintenance Phase sample size of approximately 480 patients is achieved*

The following patients may be eligible to enroll in Part 1 (OLE) of Study GA29145 during the Maintenance Phase or at Week 66:

- Patients who experience a clinical relapse, defined as meeting at least one of the following criteria on two consecutive visits (may include unscheduled visits), with at least one of the two consecutive CDAI scores ≥220:

  CDAI score ≥ the baseline (Week 0) score

  CDAI score ≥100 points higher than the Week 14 score
- Completed the Week 66 maintenance visit

4.5.9.2 Exclusion Criteria for Part 1 (OLE) of Study GA29145

The following patients are NOT eligible to enroll in Part 1 (OLE) of Study GA29145:

- Patients who leave the study before Week 10
- Patients who discontinue study drug in the Induction Phase, except for those escaping between and including Weeks 10 and 14 for disease worsening
- Patients who received medications that are prohibited in conjunction with etrolizumab (see Section 4.4.5)
- Patients with severe hypersensitivity reactions (see Section 4.3.2), malignancies, de novo or reactivated serious viral infections such as HBV, HCV, HIV, PML, or other life-threatening infections during the trial (see Section 5.1.1 and Section 4.6.2)

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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

- Patient withdrawal of consent at any time
- 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

4.6.1.1 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after withdrawing consent. Patients who withdraw from the study will not be replaced.

4.6.2 Discontinuation from Study Drug

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

- Pregnancy
- Anaphylaxis or other severe hypersensitivity reaction
- Develop colonic mucosal dysplasia
- Malignancy (with the exception of local, 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 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.
- Any medication for rescue outside defined limits of the protocol (see Section 4.4.5)

Patients who discontinue study drug prematurely for the reasons listed above will be asked to return to the clinic for an early withdrawal visit, which should take place within 4 weeks after the last dose (see Section 4.5.4 and Section 4.5.5) and will continue to undergo safety follow-up assessments for 12 weeks within this study. Patients should then enroll in Part 2 (SM) of Study GA29145 for 92 weeks of monitoring for PML (see Section 4.5.8). The primary reason for premature study drug discontinuation

should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

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

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

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

5.1.1 Potential Risks for Etrolizumab

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

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

Important potential risks for etrolizumab include:

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

5.1.1.1 Serious Infections

5.1.1.1.1 Progressive Multifocal Leukoencephalopathy

Background

PML is a potentially fatal neurological condition linked to reactivation of a polyomavirus (JCV) and active viral replication in the brain. Cases of PML have been reported in patients with CD and multiple sclerosis who received concomitant treatment with the anti-α4 integrin natalizumab and immunosuppressives. Integrin $\alpha4\beta1$, which is inhibited by natalizumab, is a pleiotropic integrin that is believed to facilitate T cell migration into the CNS. Inhibition of integrin $\alpha4\beta1$ is thought to reduce (CNS) immune surveillance and facilitate development of PML.

Etrolizumab targets cells expressing the $\beta7$ integrin ($\alpha4\beta7$ and $\alpha E\beta7$ cells) and not $\alpha4\beta1$ cells. Despite the lack of theoretical or experimental evidence for a specific role of $\beta7$ integrins in leukocyte homing to the CNS and given the observation of PML risk with natalizumab, the Sponsor will continue to conduct extensive risk-monitoring procedures during 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 *[or equivalent]*, 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 5 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 and objective tests employing the use of checklists to assess the patient's mental and neurological status. These will comprise regular neurologic examinations (including evaluation of cranial nerves, motor and sensory function, coordination, and mental status) as per the Schedule of Assessments (see Appendix 1a). The PML Subjective Checklist (symptom assessment) and the PML Objective Checklist (neurologic evaluation) will be administered (Appendix 5; Worksheet for the PML Neurologic Examination).

If a patient has a positive finding on the PML Subjective Checklist that is accompanied by a positive finding on the PML Objective Checklist or if there is strong clinical suspicion for PML, the event should be expeditiously reported to the sponsor as adverse events of special interest or serious adverse events, as appropriate, within 24 hours (see Section 5.1.1.1.1 and Appendix 6 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 CSF analysis for JCV DNA by PCR. If JCV DNA is detected, the patient should be treated as a PML case and the patient should permanently discontinue study drug and enter safety follow-up. Dosing with study drug can only be resumed in patients where PML has been ruled out. Refer to Appendix 6 for the Algorithm for Evaluation of PML.

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 5 (Worksheet for the PML Neurologic Examination) and Appendix 6 (Algorithm for the Evaluation of PML).

5.1.1.1.2 Other Serious Infections

Background

Clinical data to date have not shown an increased risk of serious infections with etrolizumab. In the Phase II EUCALYPTUS study, serious infections were reported in 2.3% of patients who received placebo versus none in the etrolizumab-treated patients. Nonetheless, serious infections are a potential risk 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 Bacille Calmette-Guerin [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 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

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

Patient Selection

Patients who 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

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

Patients should be instructed to recognize the symptoms of any anaphylactic, anaphylactoid, or hypersensitivity reaction and to contact a HCP or seek immediate care in case of any such symptoms. Patients are to be provided with alert cards to remind them and a caregiver or partner of the above.

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

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

Refer to Appendix 7 (Clinical Criteria for Diagnosis Anaphylaxis).

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.

Patient Selection

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

Education, Monitoring, and Management

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

5.1.1.4 Local Injection-Site Reactions

Background

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

Monitoring

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

5.1.1.5 Malignancies

Background

There has been no evidence for increased incidence of malignancy in completed Phase I/II trials and nonclinical studies to date. Nonetheless, given the elevated risk of malignancy in this patient population a priori, the 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 ATAs. Such antibodies can be neutralizing with potential for reducing therapeutic effect of the drug and/or sensitizing, with potential for allergic reactions. On the basis of the clinical experience to date, approximately 5% of patients develop ATAs to etrolizumab; however, this has not been correlated with any efficacy or safety sequelae.

Monitoring

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

5.1.1.7 Decreased Effectiveness of Immunizations

Background

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

Patient Selection and Risk Mitigation

Patients who received a live attenuated vaccine within 4 weeks prior randomization are not eligible for the study. Patients should not receive live attenuated vaccines during the study and for at least 5 half-lives (approximately 12 weeks) after final study drug administration.

5.1.2 Risks Associated with Worsening of Crohn's Disease

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

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

Rescue therapy with anti-TNF agents, cyclosporine, tacrolimus, sirolimus, MMF, natalizumab, vedolizumab, efalizumab, rituximab, other lymphocyte depleting agents, or

other biological or investigational therapeutics will not be allowed in conjunction with etrolizumab because of the level of immunosuppression anticipated with the use of these agents. Patients who receive any of these prohibited rescue therapies are not to receive further treatment with etrolizumab.

See Section 4.5.6, Appendix 1a, and Appendix 1b for the schedule of assessments to be performed in the event of worsening of CD, which may lead to an unscheduled visit.

5.1.3 Data Monitoring Committee

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

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.3.

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Sections 5.2.9.9 and 5.2.9.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.2.9.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] criteria; see Section 5.2.7); 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.

The investigator must report serious adverse events to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.3.2 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 5.3.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined as defined by Hy's law (see Section 5.2.9.7).
- 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 7)

  Neurological signs, symptoms, and adverse events that may suggest possible PML, on the basis of a positive finding on the PML Subjective Checklist that is accompanied by a positive finding on the PML Objective Checklist or if there is strong clinical suspicion for PML (see Appendix 5 and Section 5.1.1.1.1)

5.2.4 Methods and Timing for Capturing and Assessing Safety Parameters

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.3, 5.4, and 5.5. The investigator is also responsible for reporting medical device complaints (see Section 5.3.4).

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 5.2.7), and causality (see Section 5.2.8).

5.2.5 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsy sample collections, discontinuation of medications) should be reported (see Section 5.3.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until the patient completes his or her last study visit (in the Safety Follow-Up Phase). 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 5.5). 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 5.5).

5.2.6 Eliciting Adverse Event Information

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

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

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

5.2.7 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

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

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

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding 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.

5.2.8 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 as well as Table 3.

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (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 3 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon rechallenge.
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).

5.2.9 Procedures for Recording Adverse Events

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

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

5.2.9.1 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 as individual signs (e.g., erythema, induration/swelling at injection site) or symptoms (e.g., pain, pruritus at injection site) rather than a diagnosis of allergic reaction or injection-site reaction.

5.2.9.2 Diagnosis Versus Signs and Symptoms

For adverse events other than injection-site reactions (see Section 5.2.9.1), 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.

5.2.9.3 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.

5.2.9.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should be recorded only once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.3.2 for reporting instructions. The Adverse Event eCRF should be updated by changing the event from “non-serious” to “serious,” providing the date that the event became serious and completing all data fields related to serious adverse events.

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

5.2.9.5 Abnormal Laboratory Values

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

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

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

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens. Refer to Section 5.2.9.4.

5.2.9.6 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology

changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens. Refer to Section 5.2.9.4.

5.2.9.7 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 5.2.9.2) 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 adverse event of special interest (see Section 5.3.2).

5.2.9.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.2.5), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.3.2). This includes death attributed to progression of CD.

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

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

5.2.9.9 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").

5.2.9.10 Lack of Efficacy or Worsening of Crohn's Disease

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

5.2.9.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e. in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below. The duration of hospitalization should also be noted on the eCRF.

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not suffered an adverse event.

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

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

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

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

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

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.3.2).

5.2.9.13 Patient-Reported Outcome Data

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

5.3 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (see Section 5.3.2 for more details)
- Adverse events of special interest (see Section 5.3.2 for more details)
- Pregnancies (see Section 5.3.3 for more details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality on the basis of 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.

5.3.1 Emergency Medical Contacts

Medical Monitor Contact Information

Primary Contact

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

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

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

5.3.2.1 Events That Occur Prior to Study Drug Initiation

After informed consent has been obtained but prior to the initiation of the study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The 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.

5.3.2.2 Events That Occur after Study Drug Initiation

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

In the event that the EDC system is unavailable, the 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 post-study adverse events are provided in Section 5.5.

5.3.3 Reporting Requirements for Pregnancies

5.3.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 24 weeks after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing

the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.3.3.2 Pregnancies in Female Partners of Male Patients

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

5.3.3.3 Abortions

Any therapeutic or spontaneous abortion should be classified as a serious adverse event (because the Sponsor considers any such abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.3.2).

5.3.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly or birth defect in a child born to a female patient exposed to study drug or 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 5.3.2).

5.3.4 Reporting Requirements for Prefilled Syringe Complaints/Events

In this study, the prefilled syringe is considered a medical device. The investigator must report all medical device complaints to the Sponsor. The investigator must document as much information as possible on the PD103 IMP deviation form, including product batch number and expiration date, and forward the complaint form to the Sponsor (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 PFS, should be sent to *kaiseraugst.global_impcomplaint_management@roche.com.*

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

If the medical device 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 and submitted immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.3.2. 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.

5.4 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.4.1 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. If, after follow-up, return to baseline status or stabilization cannot be established, the adverse event outcome should be updated at Study Discontinuation.

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

5.4.2 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, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.5 POST-STUDY ADVERSE EVENTS

Patients who enter the OLE-SM study (GA29145 Parts 1 and/or 2) should follow the adverse event reporting requirements for that study.

Post-study, if the patient does not enter the OLE-SM study (GA29145 Parts 1 and/or 2), 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 (until 12 weeks after the last dose of study drug) 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 PML, regardless of relationship to study drug, for up to 2 years after the patient's last dose of study drug.

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

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

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

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

- Etrolizumab Investigator's Brochure

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

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

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

All serious related (as assessed by the investigator and/or sponsor) adverse events occurring in a patient administered etrolizumab at any time during the trial and assessed as unexpected per the reference safety information will be considered suspected unexpected serious adverse reactions (SUSARs) for the purpose of regulatory reporting

to all health authorities, with the exception of the FDA. For the FDA, SUSARs will be submitted as Investigational New Drug (IND) Safety Reports, in line with the FDA guidance "Safety Reporting Requirements for INDs and BA/BE Studies" dated December 2012.

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

For the purpose of statistical analyses, the Induction and Maintenance Phases will be treated as independent studies.

Per the protocol, the planned analysis of induction data for Cohort 1 was performed in March 2017 after the last patient in cohort 1 completed 14 weeks of treatment, and prior to the commencement of the pivotal induction cohort 3. The induction data from Cohort 1 was unblinded and evaluated in an exploratory manner to provide an early assessment of efficacy, and is treated as an independent phase II readout. The analysis provided the first data available for etrolizumab in treating Crohn's disease, and was used to confirm the statistical assumptions for the pivotal induction cohort (Cohort 3), to confirm the re-randomization rates and thus expected sample size for maintenance, and to inform the development of the Statistical Analysis Plan. Only a small number of Sponsor personnel close to the data analysis were unblinded and have knowledge of patient-level treatment assignment for Cohort 1. All remaining Sponsor personnel (including those involved in oversight of study conduct) and sites remain blinded to patient-level treatment assignment. The Sponsor remains blinded to maintenance data for all patients in the study (including cohort 1) until the maintenance database is formally cleaned, verified, and locked.

The open-label Cohort 2 serves as a feeder cohort to provide sufficient sample size for the maintenance analysis. Induction data from Cohort 2 will also be considered exploratory and may be analyzed to inform decision making and development of the Statistical Analysis Plan.

6.1 DETERMINATION OF SAMPLE SIZE

6.1.1 Induction Phase

A total of approximately 1150 patients will be randomized into one of three induction cohorts. The sample size of each cohort is summarized in Table 4 and described below.

Table 4 Sample Size for Each Cohort

Cohort	No. of Patients			
	Total	Placebo	Low-Dose (105 mg)	High-Dose (210 mg)
Exploratory induction cohort (Cohort 1)	~300	~60	~120	~120
Active-treatment induction cohort (Cohort 2)	~350	NA	~175	~175
Pivotal induction cohort (Cohort 3)	~496	~124	~186	~186

NA = not applicable; No. = number.

The sample size for Cohort 1 (see Table 4) was determined to provide approximately 90% power to detect a ≥ 20% difference in PRO2 or CDAI remission rates between each etrolizumab arm and placebo (under the assumption of placebo remission rate of ≤ 15%, similar to results reported in the GEMINI 2 trial of vedolizumab in patients with CD; Sandborn et al. 2013) and approximately 80% power to detect a 15% difference versus placebo in endoscopic response (under the assumption of placebo response rate of ≤ 10%) and a two-sided χ^2 test at the 10% significance level.

The pivotal analysis for induction phase will be performed using only patients from Cohort 3. In this pivotal induction cohort, patients will be randomized to receive either placebo, etrolizumab 105 mg or etrolizumab 210 mg in a 2:3:3 ratio. The co-primary endpoint will be tested using a CMH test at the 5% significance level, where both clinical remission and endoscopy improvement are required to be significant. The sample size for Cohort 3 is expected to provide ≥85% power to detect a ≥15% difference in rates of clinical remission (SF mean daily score ≤3 and AP mean daily score ≤1) between each etrolizumab arm and placebo under the assumption of a placebo remission rate of ≤15% and a two-sided test performed at a significance level of 5%. Additionally, Cohort 3 will provide ≥80% power to detect a 10% difference in proportions for each etrolizumab arm versus placebo for endoscopic improvement, under the assumption of placebo response rate of ≤5% and a two-sided test at the 5% significance level. The χ^2 test was used to confirm the power calculations.

Cohort 2 is sized at approximately 350 patients to achieve a sufficient number of patients for the Maintenance Phase analyses.

6.1.2 Maintenance Phase

A total of approximately 480 patients achieving CDAI-70 response at Week 14 will be eligible to enroll into the Maintenance Phase.

A co-primary endpoint will be used for the analysis of the Maintenance Phase: clinical remission (SF mean daily score ≤ 3 and AP mean daily score ≤ 1) and endoscopic improvement at Week 66. The maintenance co-primary analysis will be performed on all patients re-randomized into the Maintenance Phase who were randomized to etrolizumab (105 mg or 210 mg) in the Induction Phase. The co-primary endpoint will be tested using a CMH test at the 5% significance level, where both clinical remission and endoscopy improvement are required to be significant. Note that to maintain the blind, patients randomized to placebo in the Induction Phase will undergo a sham randomization and will receive placebo in the Maintenance Phase. These patients will not form part of the pivotal maintenance analysis.

Of the approximately 480 patients projected to be enrolled in the Maintenance Phase, approximately 420 patients will undergo re-randomization to receive either placebo or etrolizumab, and approximately 60 patients will undergo a sham randomization to placebo. These projections are based on the assumption that 50% of patients receiving etrolizumab and 40% of patients receiving placebo during the Induction Phase will be eligible for the Maintenance Phase.

Assuming a maintenance sample size of *210* patients per arm using a 1:1 allocation to receive either placebo or etrolizumab 105 mg, the maintenance analyses conducted at the 5% significance level will provide the following power:

- Clinical remission at Week 66 (SF mean daily score ≤3 and AP mean daily score ≤1): at least 90% power to detect a 15% treatment difference assuming a placebo Week 66 remission rate of up to 20%
- Endoscopic improvement: *approximately* 90% power to detect a 15% treatment difference assuming a placebo Week 66 improvement rate of up to 30%

Furthermore, the study is designed to provide sufficient power for the following secondary analyses:

- Clinical remission at Week 66 among patients achieving clinical remission at Week 14: a sample size of N=*186* (i.e., *93* per arm) will provide 80% power to detect a 20% treatment difference assuming a placebo rate of up to 30%. This assumes a Week 14 clinical remission rate of ≥22% among etrolizumab patients

Table 5 Power Estimates for Primary and Key Secondary Efficacy Analysis in the Pivotal Induction Phase and Maintenance Phase

Study	Endpoint	Power	Assumed Response Rates	Sample Size per Group
Induction	Clinical remission	≥85%	Placebo = 15% Etrolizumab = 30%	Placebo = 124 Etrolizumab 105 mg = 186 Etrolizumab 210 mg = 186
	Endoscopic improvement	≥80%	Placebo = 5% Etrolizumab = 15%	Placebo = 124 Etrolizumab 105 mg = 186 Etrolizumab 210 mg = 186
Maintenance	Clinical remission	≥90% [a]	Placebo ≤ 20% Etrolizumab ≤35%	Placebo = *210* Etrolizumab 105 mg = *210*
	Endoscopic improvement	~90% [a]	Placebo ≤30% Etrolizumab = 45%	Placebo = *210* Etrolizumab 105 mg = *210*

All analyses powered using type I error, $\alpha = 5.0\%$.

[a] Analysis conducted on all patients in Maintenance Phase who were randomized to etrolizumab in the Induction Phase.

6.2 SUMMARIES OF CONDUCT OF STUDY

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

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics such as age, sex, race, region, use of corticosteroids and immunosuppressants, anti-TNF therapy, duration of disease, extent of disease, average daily SF, average daily AP, CDAI, SES-CD, [redacted] and [redacted] will be summarized for all randomized patients by treatment arm with use of descriptive statistics for both the Induction and Maintenance Phases. Exposure to study drug (number of study treatments and duration of treatment) will be summarized by treatment arm.

6.4 EFFICACY ANALYSES

For the purpose of statistical analyses, the Induction and Maintenance Phases will be treated as independent studies.

Patients who are non-evaluable for efficacy at a specific time point, because of missing data, will be considered non-responders for all categorical endpoints. In addition, patients requiring rescue therapy, and/or surgical intervention for CD, and/or took prohibited medications (see Section 4.4.5), will be considered non-responders for the

analysis. Non-responder definitions will be further detailed and finalized in the Statistical Analysis Plan for the study.

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

- Subgroup analyses to evaluate the consistency of results across prespecified subgroups (including baseline anti−TNF-status, baseline CS status, baseline IS status, age, sex, [redacted], Region
- Sensitivity analyses to evaluate the robustness of results to the primary analysis methods (e.g., handling of dropouts, adjusting for cohort)

6.4.1 Induction Phase

Efficacy analyses for the Induction Phase will be performed separately for each cohort, and will include all patients who were randomized and received at least one dose of study drug (modified intent-to-treat population [mITT]). Patients will be grouped according to the treatment assigned at randomization.

6.4.1.1 Cohort 1

An exploratory analysis was conducted when all patients in Cohort 1 (n = 300) completed the Week 14 visit or, discontinued early from the study. At this point, the Sponsor was unblinded to patient level data and treatment assignments for patients in Cohort 1 Induction Phase only. Patients, site monitors, and investigators remain blinded to patient-specific treatment assignments. The induction data from Cohort 1 was exploratory in nature and was evaluated prior to the commencement of enrollment to the pivotal Induction Phase of Cohort 3. Maintenance phase data from Cohort 1 patients will form part of the pivotal maintenance phase analysis and remains blinded to all Sponsor personnel and sites until the database lock.

6.4.1.2 Cohort 2

Cohort 2 is considered a “feeder” cohort to help achieve the necessary sample size for the maintenance study. All primary and secondary efficacy parameters will be summarized descriptively for each treatment arm. Demographic and baseline characteristics such as age, sex, race, region, use of corticosteroids and immunosuppressants, duration of disease, and CD activity scores will be summarized for each treatment group by use of descriptive statistics.

6.4.1.3 Cohort 3

The co-primary endpoint analysis will compare for each etrolizumab dose arm versus the placebo arm the proportion of patients who achieve clinical remission or endoscopic improvement at Week 14.

The difference between each etrolizumab arm and placebo arm will be evaluated using the CMH test statistic stratified by the factors used at randomization. The absolute treatment difference will be provided along with the 95% two-sided CI estimate.

All categorical secondary endpoints will be analyzed using the same methodology as the primary endpoint. For all efficacy endpoints, descriptive summary statistics will be provided for each treatment arm.

Continuous endpoints will be analyzed using an ANCOVA model with the stratification variables used at randomization and the baseline value of the studied measure as a covariate.

The co-primary endpoints will each be tested at the 5% significance level, with both required to be significant for the co-primary endpoints to be deemed significant. The overall type I error rate will be maintained at 5% using a hierarchical model for testing of the two etrolizumab doses versus placebo and corresponding key secondary endpoints. The hierarchical model specifications will be detailed in the Statistical Analysis Plan before unblinding. The remaining secondary endpoints [redacted] will be considered to provide supportive information and no adjustments for multiple comparisons will be performed.

6.4.2 Maintenance Phase

Efficacy analyses for the Maintenance Phase will include all etrolizumab induction patients who were randomized into the Maintenance Phase and received at least one dose of study drug (mITT population). Patients will be grouped according to the treatment assigned at randomization into the Maintenance Phase.

For all categorical endpoints, the difference in proportions between the two treatment arms will be evaluated using the CMH test. The CMH test will include important stratification factors such as those used to randomize patients into the Maintenance Phase. The stratification factors used for re-randomization into the maintenance phase include sustained CDAI remission at Weeks 10 and 14. As a result of the changes to endpoints introduced in Protocol Version 6, this stratification factor in the analysis will be replaced with clinical remission at Week 14 for the clinical remission at Week 66 analysis, and endoscopic improvement at Week 14 for the endoscopic improvement at Week 66 analysis. A sensitivity analysis will be conducted to include the sustained CDAI stratification factor used at randomization. The test will be performed at the two-sided 5% significance level. The absolute treatment difference will be provided along with the 95% two-sided CI estimate. All categorical secondary endpoints will be analyzed using the same methodology as for the primary endpoint.

Continuous endpoints will be analyzed using an ANCOVA model with the stratification variables used at randomization and the baseline value of the studied measure as a covariate.

If the primary endpoint is statistically significant, key secondary endpoints will be tested sequentially. Details will be specified in the Statistical Analysis Plan before unblinding.

Patients who are non-evaluable for efficacy at a specific timepoint (e.g., because of missing data or early enrollment into Part 1 [OLE] of Study GA29145) will be considered non-responders for all categorical endpoints.

6.4.3 Co-Primary Efficacy Endpoints

Induction Phase

- Proportion of patients in clinical remission at Week 14
- Proportion of patients achieving endoscopic improvement at Week 14

Maintenance Phase*, among patients who achieve CDAI-70 response at Week 14*

- Proportion of patients in clinical remission at Week 66
- Proportion of patients achieving endoscopic improvement at Week 66

6.4.4 Secondary Efficacy Endpoints

The secondary endpoints are as follows:

Induction Phase

- Proportion of patients who achieve clinical remission at Week 6
- Proportion of patients who achieve SES-CD ≤4 (≤2 for ileal patients), with no segment having a subcategory score (i.e., for ulceration size and extent, affected surface, or narrowing) that is >1, at Week 14
- Changes from baseline to Week 14 in CD-PRO/SS score

Maintenance Phase

- Proportion of patients in clinical remission at Week 66 among patients who achieve clinical remission at Week 14
- Proportion of patients who achieve corticosteroid-free clinical remission at Week 66 *among patients who were receiving corticosteroids at baseline*
- Proportion of patients who maintain endoscopic improvement at Week 66 among patients achieving endoscopic improvement at Week 14
- Proportion of patients achieving SES–CD ≤4 (≤2 for ileal patients), with no segment having a subcategory score (i.e., for ulceration size and extent, affected surface, or narrowing) that is >1, at Week 66
- Proportion of patients achieving durable remission
- Proportion of patients achieving corticosteroid-free clinical remission for 24 weeks at Week 66 *among patients who were receiving corticosteroids at baseline*
- Change from baseline to Week 66 in CD-PRO/SS score

Secondary endpoints for the Maintenance Phase will be assessed in the group of patients who were randomized into the Maintenance Phase, unless otherwise specified.

[redacted]

6.5 SAFETY ANALYSES

In each of the induction cohorts (open-label etrolizumab, blinded etrolizumab, or blinded placebo), the safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to the treatment and dose actually received (etrolizumab high- or low-dose, blinded etrolizumab high- or low-dose, or placebo).

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

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

6.5.1 Adverse Events

Verbatim descriptions of treatment-emergent adverse events will be coded and their incidence will be summarized by treatment arm, as appropriate. A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an

existing condition on or after the first dose of study drug. In addition, separate summaries will be generated for serious adverse events, deaths, and adverse events leading to discontinuation of study drug.

Analyses will also be performed for:

- Systemic hypersensitivity events

  Specific analyses will be performed for anaphylactic reactions.

- Serious infections

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

- Opportunistic infections

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

- Malignancies

  Events of malignancy will also be summarized for each treatment arm.

- Injection-site reactions

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

- Surgery for CD

  The time to onset of surgery for CD complications will be summarized for each treatment arm.

6.5.2 Laboratory Tests

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

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

6.6 PHARMACOKINETIC, PHARMACODYNAMIC, [redacted] ANALYSES

Serum concentration at various specified timepoints during the Induction and Maintenance Phases 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.

All drug concentration data collected from this study will be included in a model–based analysis that uses a non-linear mixed effect model–based approach to further characterize the PK and relevant influential factors. The model–based analysis will be reported separately from the main clinical study report.

[redacted]

[redacted]

6.7 OPTIONAL INTERIM ANALYSIS

The Sponsor may choose to conduct an interim analysis. The interim analysis will involve unblinding of treatment assignments to the Sponsor for purposes of data analysis and interpretation. Patients and all study site personnel will remain blind to individual patient-level treatment assignments until completion of the trials. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel, who will be unblinded at the treatment group level.

The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. Access to treatment assignment information will follow the Sponsor's standard procedures.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor, CRO, and Data Management vendor will be responsible for data management of this study, including quality checking of the data. Sites will be responsible for data entry into the EDC system with use of eCRFs. In the event of discrepant data, data queries will be issued to the sites and resolved by the sites via the EDC system. The Sponsor will produce a data quality plan that will describe the quality checking to be performed on the data. eCRFs and correction documentation will be maintained in the EDC system's audit trail.

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

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to Help Text in the Medidata RAVE system for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

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

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

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patient-reported data will be collected using an electronic devices provided by an ePRO vendor. The devices (i.e., e-diary and tablet) are designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA regulations for electronic records (21 CFR Part 11). The ePRO device data are available for view access only via secure access to a Web portal provided by the ePRO vendor. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures. Regular data transfers will occur from the centralized database at the vendor to the database at the Sponsor.

Once the study is complete, the ePRO data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all patient data in a machine-readable format on a compact disc.

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

7.4 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, 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 7.6.

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

7.5 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.

7.6 RETENTION OF RECORDS

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the International Council for Harmonisation (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 an IND will comply with 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 Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "consent forms") before IRB/EC submission. The final IRB/EC–approved consent forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

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

Patients must be re-consented to the most current version of the consent forms (or to a significant new information/findings addendum in accordance with applicable laws and

IRB/EC policy) during their participation in the study. For any updated or revised consent forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised consent forms for continued participation in the study.

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, 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 is sponsored by F. Hoffmann–La Roche Ltd. Approximately 500 global investigator sites will participate in this study to enroll approximately 1150 patients.

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

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

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

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

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

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments on the basis of 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: Screening and Induction Phase

Assessment Category	Assessments	Screening Day [a] −35 to −1	Study Week (± 3 days for Weeks 2, 4, 8, and 12; ± 7 days for Weeks 10 and 14)							UV [c]	Early WD (± 7 days)
			0 [b]	2	4	8	10	12	14		
Screening only Assessments	Informed consent	x									
	Demographic data	x									
	Height	x									
	Medical History	x									
	Chest x-ray [d]	x									
	TB screen [e]	x									
	Hepatitis C serology	x									
	HIV test	x									
	Plasma sample (Storage for JCV antibody testing) [1]	x									
Study Drug	Initial randomization		x								
	Study drug administration [f]		x	x	x	x		x			

Appendix 1a
Schedule of Assessments: Screening and Induction Phase (cont.)

Assessment Category	Assessments	Screening Day [a] −35 to −1	Study Week (± 3 days for Weeks 2, 4, 8, and 12; ± 7 days for Weeks 10 and 14)							UV [c]	Early WD (± 7 days)
			0 [b]	2	4	8	10	12	14		
Assessments at Screening and Induction	Review eligibility criteria	x	x [g]								
	Concomitant medications	x	x	x	x	x	x	x	x	x	x
	Adverse events [h]	x	x	x	x	x	x	x	x	x	x
	e-Diary check [i]	x	x	x	x	x	x	x	x	x	x
	Pregnancy test [j]	x	x [g]	x	x	x		x			x
	CDAI assessment	x	x [k]				x		x	x	x [l]
	Weight	x	x				x		x	x	x
	PML assessment interview [m]	x			x				x	x	x
	Neurological examination [m]	x			x				x	x	x
	Vital signs (BP and pulse)	x	x [g]		x	x		x			x
	Physical examination [n]	x							x		x
	Fistula examination [o]	x							x		x
	ECG	x	x [p]								x
	[redacted] [q]		x						x		x
	[redacted] [q]		x						x		
	Stool sample	x [r, s]							x [s]		x [s, t]
	Ileocolonoscopy [u]	x							x	x	x [t, v]
	Ileum/colon biopsies (formalin)	x [w]							x [x]		x [t, v, x]
	Ileum/colon biopsies (RNAlater)	x [w]							x [x]		x [t, v, x]

Appendix 1a
Schedule of Assessments: Screening and Induction Phase (cont.)

Assessment Category	Assessments	Screening Day [a] –35 to –1	Study Week (± 3 days for Weeks 2, 4, 8, and 12; ± 7 days for Weeks 10 and 14)							UV [c]	Early WD (± 7 days)
			0 [b]	2	4	8	10	12	14		
Laboratory Assessments	Hematology	x	x [g]		x [y]	x [y]	x [y]		x	x	x [v]
	Chemistry	x	x [g]						x	x	x [v]
	Serum sample ([redacted])	x	x		x	x			x		x [v]
	Hepatitis B serology	x							x [z]		
	Urinalysis	x	x [g]							x	
Required PK/PD Blood Draw	Population PK sampling (serum) [aa]		x				x		x		x
	[redacted]	x	x				x		x		x
	[redacted]	x	x		x		x		x		x
	ATA sample (serum) [aa, cc]		x		x				x	x	x
Optional Banking Sample	Whole blood DNA (optional)		x								
Optional PK/PD Substudy Sample	Refer to Appendix 3										

ATA = anti-therapeutic antibodies; BP = blood pressure; CD = Crohn's disease; CD–PRO/SS = Crohn's Disease Patient–Reported Outcome Signs and Symptoms; CDAI = Crohn's Disease Activity Index; [redacted] eCRF = electronic case report form; [redacted]; HBV = Hepatitis B virus; HCP = health care professional; [redacted]; INF-γ = interferon gamma; PD = pharmacodynamic; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy; PPD = purified protein derivative; qPCR = quantitative polymerase chain reaction; TB = tuberculosis; UV = unscheduled visit; WD = withdrawal.

Notes: Study assessments and blood draws are to be conducted prior to study drug administration.
All biopsy samples will be taken during endoscopy procedure.

Appendix 1a
Schedule of Assessments: Screening and Induction Phase (cont.)

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

[b] Day 1 of Week 0. Visit window of ± 3 days does not apply.

[c] An unscheduled visit is required for an adverse event, serious adverse event or can be undertaken to evaluate a patient for ongoing signs and symptoms of CD that potentially require rescue therapy, or can be used to evaluate potential clinical relapse. All the listed assessments do NOT have to be performed at an unscheduled visit; assessments should be symptom-driven (e.g., perform PML assessment interview and neurological examination only if patient reports symptoms suspected of PML). Assessments corresponding to items noted in this column should be recorded on the eCRF.

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

[e] The following tests are acceptable screening assays for latent TB in this study: PPD (a tuberculin skin test reaction; e.g., Mantoux test), INF-γ based test (e.g., QuantiFERON®-TB Gold). Only one of these screening assays is required.

[f] All patients will receive one 0.7-mL injection and one 1.4-mL injection of Weeks 0, 4, 8, and 12. On Week 2, all patients will receive one 1.4-mL injection.

[g] Perform prior to randomization.

[h] After informed consent has been obtained but prior to the initiation of study drug, only serious adverse events cause by a protocol-mandated intervention (e.g., invasive procedure such as biopsy sample collections, discontinuation of medications) should be reported. After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until the patient completes his or her last visit.

[i] Patients are to complete the e-diary daily for frequency of loose/liquid stools, abdominal pain (including the APQ), and general well-being. Patients will complete the CD–PRO/SS measure for at least 9 consecutive days around each visit as programmed in the e-diary. In order to allow for the visit window to account for early or delayed visits, patients may complete the CD–PRO/SS up to 12 days, except for the Week 0 visit in which patients are to complete the CD-PRO/SS on a daily basis for the 9 days before the Week 0 visit.

[j] Serum screening test for all females except those who are > 1-year postmenopausal or surgically sterile; perform a urine test at other visits. If urine test result is positive, perform confirmatory serum test. Patients must be instructed at screening and reminded throughout the study that in case of positive pregnancy test result they must call the site immediately. Do not administer etrolizumab unless the serum test result is negative.

[k] The patient will complete the PRO components of the CDAI on the e-diary daily during the screening phase. The blood draw for the hematocrit component can occur at any time during screening and the screening hematocrit value will be used for the Week 0 CDAI calculation. The physician assessment components of the CDAI score will be assessed at the Week 0 visit. The CDAI score for eligibility will be calculated at the Week 0 visit prior to randomization.

Appendix 1a
Schedule of Assessments: Screening and Induction Phase (cont.)

[l] Patients withdrawing from the study within 2 weeks after Weeks 10 or 14 do not need to repeat the CDAI assessment as part of the early withdrawal visit.

[m] Administer before other assessments.

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

[redacted]

[p] If the ECG was not performed during screening, it must be performed at the Week 0 visit prior to randomization.

[redacted]

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

[redacted]

[t] Patients withdrawing from the study within 4 weeks of the Week 14 visit do not need to repeat the ileocolonoscopy, stool sample, and biopsies as part of the early withdrawal visit. Patients withdrawing between 4 to 8 weeks of the Week 14 visit should repeat the ileocolonoscopy, stool sample, and biopsies as part of the early withdrawal visit, unless there is strong objection by the investigator.

[u] Video-recorded and centrally-read ileocolonoscopy. Screening ileocolonoscopy is to be undertaken within the Screening period and at least 9 days prior to randomization. For the Week 14 and 66 visit, the ileocolonoscopy should be scheduled on the day of the visit. If this is not possible, the ileocolonoscopy must be performed no later than 5 days after the visit.

[v] Not required if early withdrawal was after an unscheduled visit and the assessment was undertaken at that unscheduled visit.

[w] A total of nine pairs (18 biopsy samples) will be obtained during screening. Two pairs will be placed in stabilization buffer (RNAlater; one pair per tube) and stored at –80°C. The other seven pairs (which include 2 pairs of sigmoid and 1 pair of transverse colon biopsies) will be placed in formalin at the sites and sent to the central laboratory to be paraffin embedded and for further storage or distribution.

[x] A total of six pairs (12 biopsy samples) will be obtained. All will be sent to the central laboratory to be paraffin embedded and for further storage or distribution. One pair will be placed in a stabilization buffer (RNAlater and stored at –80°C. The five other pairs (which include 2 pairs of sigmoid and 1 pair of transverse colon biopsies) will be placed in formalin at the sites and sent to the central laboratory to be paraffin embedded and for further storage or distribution.

[y] Hematocrit only.

Appendix 1a
Schedule of Assessments: Screening and Induction Phase (cont.)

[z] Enrolled patients who are HBV core antibody positive should have HBV DNA measured at Week 14.

[redacted]

[redacted]

[cc] At all timepoints indicated and whenever serum sickness or a clinically significant allergic drug reaction is suspected. [redacted]

[1] 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.

Appendix 1b
Schedule of Assessments: Maintenance Phase

Assessment Category	Assessments	Week 14 (Last Induction Visit)	Study Week (± 3 days, except for Week 66, for which the window is ± 7 days)														UV [b]	Early WD (± 7 days)
			16	20 [a]	24	28	32	36 [a]	40 [a]	44	48[a]	52 [a]	56	60[a]	64[a]	66		
Study Drug	Re-randomization		x [c]															
	Study drug administration		x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]			
Assessments at Maintenance	Concomitant medications	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
	Adverse events	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
	e-Diary check [e]	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
	Pregnancy test [f]		x	x	x	x	x	x	X	x	x	x	x	x	x			x
	CDAI assessment	x			x	x	x			x			x			x	x	x
	Weight	x			x	x	x			x			x			x	x	x
	PML assessment interview [g]	x			x		x			x			x			x	x	x
	Neurological examination [g]	x			x		x			x			x			x	x	x
	Vital signs (BP and pulse)		x		x		x			x			x			x		x
	Physical examination [h]	x			x		x			x			x			x		x
	[redacted]	x			x		x			x			x			x		x
	ECG		x													x		x
	[redacted]	x								x						x		x
	[redacted]	x								x						x		
	Stool sample	x [k]														x [k]		x

Appendix 1b
Schedule of Assessments: Maintenance Phase (cont.)

Assessment Category	Assessments	Week 14 (Last Induction Visit)	Study Week (± 3 days, except for Week 66, for which the window is ± 7 days)														UV [b]	Early WD (± 7 days)
			16	20 [a]	24	28	32	36 [a]	40 [a]	44	48[a]	52 [a]	56	60[a]	64[a]	66		
Assessments at Maintenance (cont.)	Ileocolono-scopy [l]	x														x	x	x [m, n]
	Ileum/colon biopsies (formalin)	x[m]														x [n]		x [m, n, o]
	Ileum/colon biopsies (RNAlater)	x[o]														x [m]		x [m, n, o]
Laboratory Assessments	Hematology	x			x	x [p]	x [p]			x			x [p]			x	x	x [m]
	Chemistry	x			x					x						x	x	x [m]
	Serum sample ([redacted])	x														x		x [m]
	Hepatitis B serology	x [r]			x [r]		x [r]			x [r]			x [r]			x [r]		
	Urinalysis																x	
Required PK/PD Blood Draw	Population PK sampling (serum) [s]	x	x		x	x	x			x						x		x
	[redacted]	x	x		x	x	x			x						x		x
	[redacted]	x			x		x			x						x		x
	ATA sample (serum) [s, u]	x			x		x			x						x	x	x
Optional	Refer to Appendix 3																	

Appendix 1b
Schedule of Assessments: Maintenance Phase (cont.)

Assessment Category	Assessments	Week 14 (Last Induction Visit)	Study Week (± 3 days, except for Week 66, for which the window is ± 7 days)														UV [b]	Early WD (± 7 days)
			16	20 [a]	24	28	32	36 [a]	40 [a]	44	48 [a]	52 [a]	56	60 [a]	64 [a]	66		
PK/PD Substudy Sample																		

ATA = anti-therapeutic antibodies; BP = blood pressure; CD = Crohn's disease; CD–PRO/SS = Crohn's Disease Patient -Reported Outcome Signs and Symptoms; CDAI = Crohn's Disease Activity Index; [redacted]; eCRF = electronic case report form; [redacted]; HBV = Hepatitis B virus; HCP = health care professional; [redacted]; INF-γ = interferon gamma; PD = pharmacodynamic; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy; PPD = purified protein derivative; qPCR = quantitative polymerase chain reaction; TB = tuberculosis; UV = unscheduled visit; WD = withdrawal.

Notes:

- Study assessments and blood draws are to be conducted prior to study drug administration.
- All biopsy samples will be taken during endoscopy procedure.

[a] Telephone visit

[b] An unscheduled visit is required for an adverse event, serious adverse event or can be undertaken to evaluate a patient for ongoing signs and symptoms of CD that potentially require rescue therapy, or can be used to evaluate potential clinical relapse. All the listed assessments do NOT have to be performed at an unscheduled visit; assessments should be symptom-driven (e.g., perform PML assessment interview and neurological examination only if patient reports symptoms suspected of PML). Assessments corresponding to items noted in this column should be recorded on the eCRF.

[c] The randomization call to IxRS can be made between Weeks 14 and 16, once a patient is confirmed eligible for the maintenance study.

[d] Where indicated, patients must be instructed to administer study drug at home within ±3 days after clinic unless the patients requests that study drug be administered by HCP at the clinic *or a PK blood draw is planned*.

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[e] Patients are to complete the e-diary daily for frequency of loose/liquid stools, abdominal pain (including the APQ), and general well-being.

Appendix 1b
Schedule of Assessments: Maintenance Phase (cont.)

Patients will complete the CD–PRO/SS measure for at least 9 consecutive days around each visit as programmed in the e-diary. In order to allow for the visit window to account for early or delayed visits, patients may complete the CD–PRO/SS up to 12 days. Female patients are also required to enter the results of their urine pregnancy test

[f] Urine test. If urine test is positive, perform confirmatory serum test. Urine test can be carried out at home during telephone visit. Patient is to report the pregnancy test result via e-diary. Patients must be instructed throughout the study that in case of positive pregnancy test result they must stop self-administration of study drug and call the site immediately. Do not administer etrolizumab unless the serum test result is negative.

[g] Administer before other assessments.

[h] Symptom-driven physical examination.

[redacted]

[l] Video-recorded and centrally-read ileocolonoscopy.

[m] Not required if early withdrawal was after an unscheduled visit and the assessment was undertaken at that unscheduled visit.

[n] Patients withdrawing from the study after the Week 66 visit do not need to repeat the ileocolonoscopy, stool sample, and biopsies at the early withdrawal visit.

[o] A total of six pairs (12 biopsy samples) will be obtained. One pair will be placed in a stabilization buffer (RNAlater) and stored at –80°C. The other five pairs (which include 2 pairs of sigmoid and 1 pair of transverse colon biopsies) will be placed in formalin at the sites and sent to the central laboratory to be paraffin embedded and for further storage or distribution.

[p] Hematocrit only.

[r] Enrolled patients who are HBV core antibody positive should have HBV DNA measured at these visits.

[redacted]

Appendix 2 Schedule of Assessments for 12-Week Safety Follow-Up

Assessment	Week (±3 days)		Unscheduled Visit [c]
	6 [a]	12/Early Withdrawal [b]	
PML assessment interview [d]		x	x [e]
Neurological examination [d]		x	x [e]
Anti-therapeutic antibody sample (serum) [f]		x	
Urine pregnancy test [g]		x	
Medication changes	x	x	x
Adverse events	x	x	x

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

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

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

[c] Unscheduled visit for safety monitoring.

[d] Administer before other assessments.

[e] If clinically indicated.

[f] At all timepoints indicated and whenever serum sickness is expected. [redacted]

[g] Urine pregnancy test. If urine test is positive, perform confirmatory serum test.

Appendix 3 Schedule of Assessments: All Optional PK/PD Substudy Samples

Assessments	Screening Day [a] −35 to −1	Study Week (±3 days)																				Unscheduled Visit	Early Withdrawal
		0 [b]	2	4	8	10	12	14	16	20 [c]	24	28	32	36 [c]	40 [c]	44	48 [c]	52[c]	56	60[c]	64[c]	66	
Substudy PK sample [d, e] (Serum)		x [f] Baseline not required. **Sample to be taken on one of Days 3/4/5 post-visit**	x	x			x [e, f] At visit AND one of Days 3/4/5 post visit			x													x
Substudy PD sample [d, e] (whole blood, FACS tube)	x	x [f] Baseline AND one of Days 3/4/5 post visit		x		x		x	x	x	x	x											
Substudy PD sample [d, e] (serum)		x [f] Baseline not required. Sample to be taken on one of Days 3/4/5 post-visit	x	x						x													x

Appendix 3 Schedule of Assessments: All Optional PK/PD Substudy Samples (cont.)

FACS = fluorescence-activated cell sorting; PD = pharmacodynamics; PK = pharmacokinetic.

These samples are to be collected only in those patients who consent for the PK/PD substudy, in addition to the samples collected for the main study (see Appendix 1).

Samples for PK/PD sub-study will be collected in approximately 150 *evaluable* patients participating in the PK/PD substudy (see footnote f, below)

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

[b] Day 1 of Week 0.

[c] Telephone visit: Blood draws may be collected by appropriately qualified personnel in the patient's home or other suitable location away from the clinic. If samples are not collected at the clinic, samples will be sent on the day of collection to a central laboratory for storage until analysis begins.

[d] Only for patients who consent to participate in PK/PD substudy.

[e] Samples are to be collected prior to dose administration *(if specified sample collection timepoint is a dosing date.*

[f] For patients participating in the PK/PD substudy, an additional blood draw will be required; this can take place 3, 4, or 5 days after the baseline visit with the first dose and after the dose on Week 12 visit. The additional blood draws should be collected by appropriately qualified personnel in the patient's home or other suitable location away from the clinic. If samples are not collected at the clinic, samples should be sent on the day of collection to a central laboratory for storage until analysis begins.

Appendix 4 Childbearing Potential, Pregnancy Testing, and Contraception

All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening and a urine pregnancy test prior to administration of study drug at subsequent visits. If a urine pregnancy test result is positive, study drug will not be administered until pregnancy is ruled out. The result must be confirmed by a serum pregnancy test (conducted by the central laboratory). Refer to Section 5.3.3 of the protocol for management of a patient with a confirmed pregnancy.

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

For 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.

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

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

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

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 12 weeks after the last dose of study drug. Men must refrain from donating sperm during this same period.

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

Appendix 5 Worksheet for the PML Neurologic Examination

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

PML usually manifests with subacute, progressive neurologic deficits including:

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

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

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

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

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

PML Subjective Checklist

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

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

PML Objective Checklist

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

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

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

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

Please complete the PML eCRF.

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

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

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

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

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

Is PML suspected? (Yes/No)

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

1. Visual fields and ocular motility

Visual Field Testing:

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

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

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

Ocular Motility Testing:

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

2. Speech

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

3. Strength

Pronator drift test (Barre maneuver):

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

Gait testing:

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

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

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

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

4. Coordination

Tandem gait:

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

Finger to nose:

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

5. Comprehension

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

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

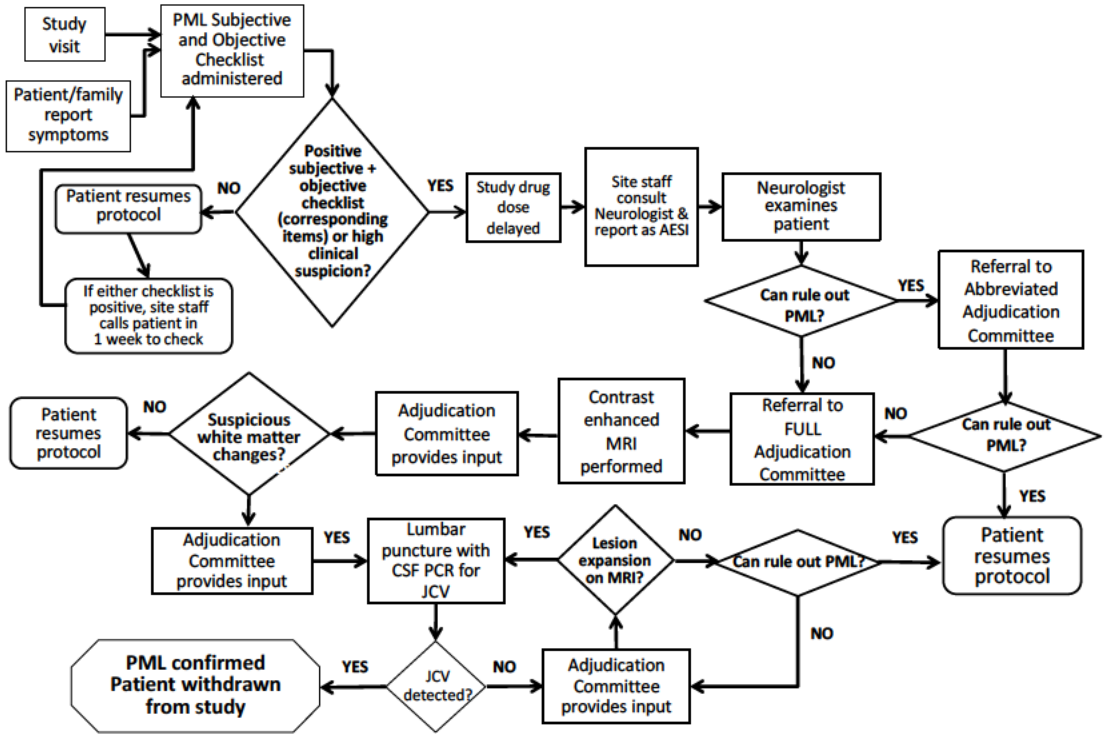
6. Memory and Thinking

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

7. Sensation

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

Appendix 6 Algorithm for the Evaluation of Progressive Multifocal Leukoencephalopathy



Appendix 7 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)
- 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)

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

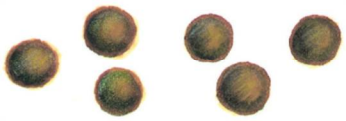
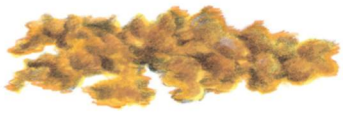
- Infants and children: low systolic blood pressure (age specific)[2] or greater than 30% decrease in systolic blood pressure
- Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline

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

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

Appendix 8 Bristol Stool Form Scale

THE BRISTOL STOOL FORM SCALE

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

Appendix 9 Crohn's Disease Activity Index (CDAI)

Category	Count	Initial Total	Multiplication Factor	Total
Number of liquid or very soft stools	7-day total number of liquid or very soft stools (reported on the 7 days immediately prior to the study visit)		× 2	
Abdominal pain	7-day total of daily abdominal pain scores on a 3-point scale: 0=none, 1=mild, 2=moderate, 3=severe (reported on the 7 days immediately prior to the study visit)		× 5	
General well being	7-day total of daily general well-being scores on a 4-point scale: 0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible (reported on the 7 days immediately prior to the study visit)		× 7	
Extra-intestinal manifestations of Crohn's Disease	Total number of checked boxes (check **all** that apply): ☐ Arthritis/arthralgia ☐ Iritis/uveitis ☐ Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis ☐ Anal fissure, fistula, or abscess ☐ Other fistula ☐ Fever over 37.8°C during past week		× 20	
Lomotil/Imodium/opiates for diarrhea	Yes = 1 No = 0		× 30	
Abdominal mass	None = 0 Questionable = 2 Definite = 5		× 10	
Hematocrit (%)[a]	Males: subtract value from 47 Females: subtract value from 42		× 6	
Body Weight[b]	(1 – (Body weight/ Standard Weight)) × 100		× 1	
Final Score			Add totals:	

a If hematocrit subtotal <0, enter 0.

b If body weight subtotal <-10, enter -10.

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

Appendix 10 Simple Endoscopic Score for Crohn's Disease (SES–CD)

Table 1 Definitions of Simple Endoscopic Score for Crohn's Disease

	Simple Endoscopic Score for Crohn's Disease values			
Variable	**0**	**1**	**2**	**3**
Size of ulcers	None	Aphthous ulcers (Ø 0.1 to 0.5 cm)	Large ulcers (Ø 0.5 to 2 cm)	Very large ulcers (Ø > 2 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Ø, Diameter.

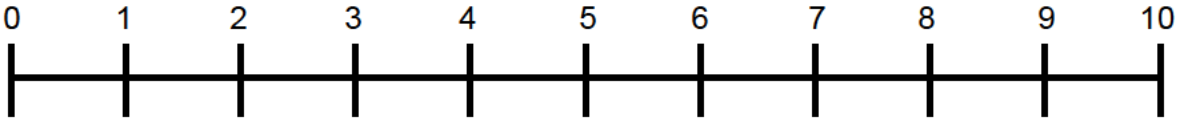
Table 2 Example of SES–CD scoring form

	Ileum	Right colon	Transverse colon	Left colon	Rectum	Total
Presence and size of ulcers (0-3)						
Extent of ulcerated surface (0-3)						
Extent of affected surface (0-3)						
Presence and type of narrowings (0-3)						
					SES-CD =	

Adapted from: Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES–CD. Gastrointestinal Endoscopy 2004; 60:505-512.

Appendix 11 Abdominal Pain Questionnaire (APQ)

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

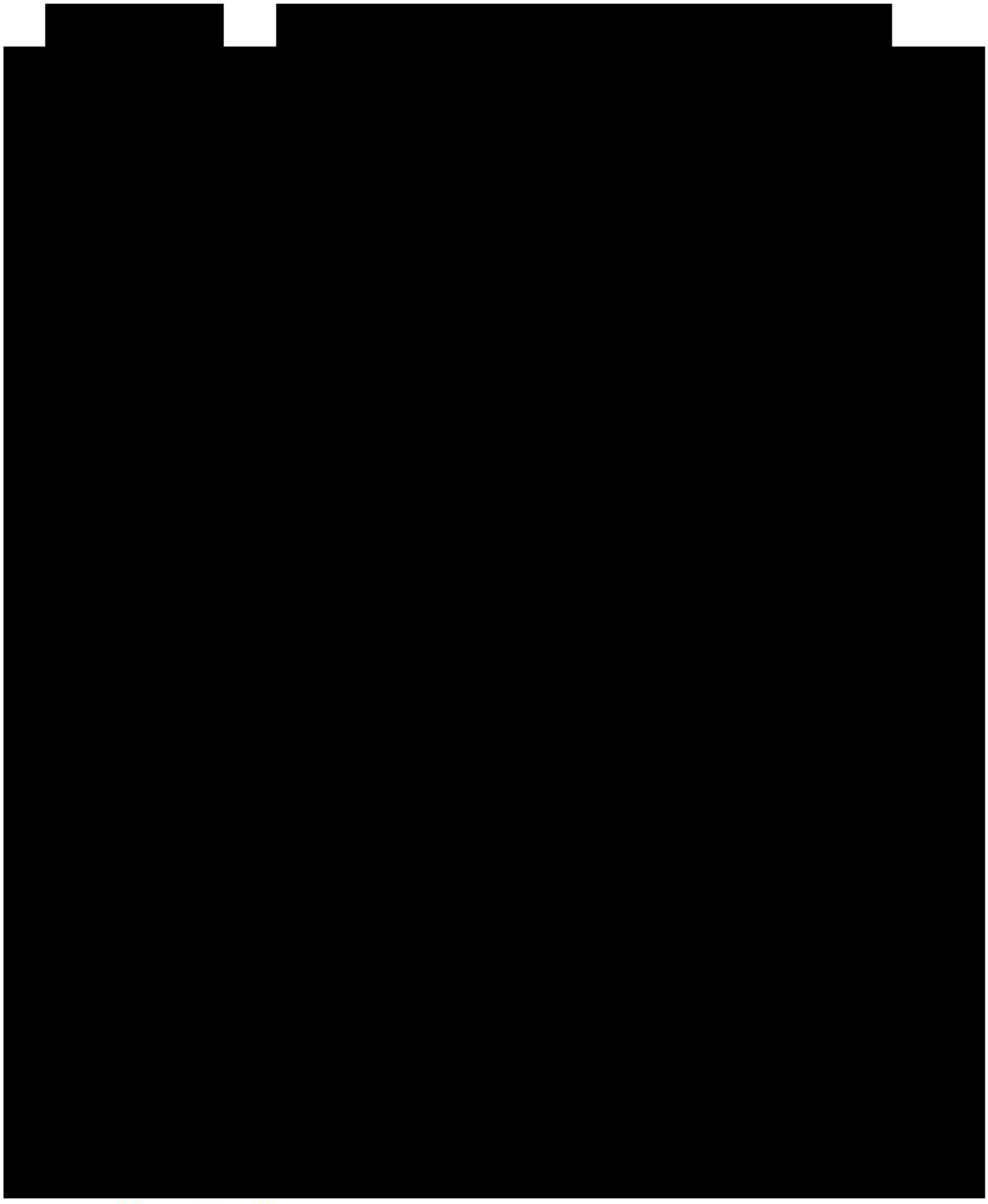


None

Pain as bad as you can imagine

[redacted]

[redacted]



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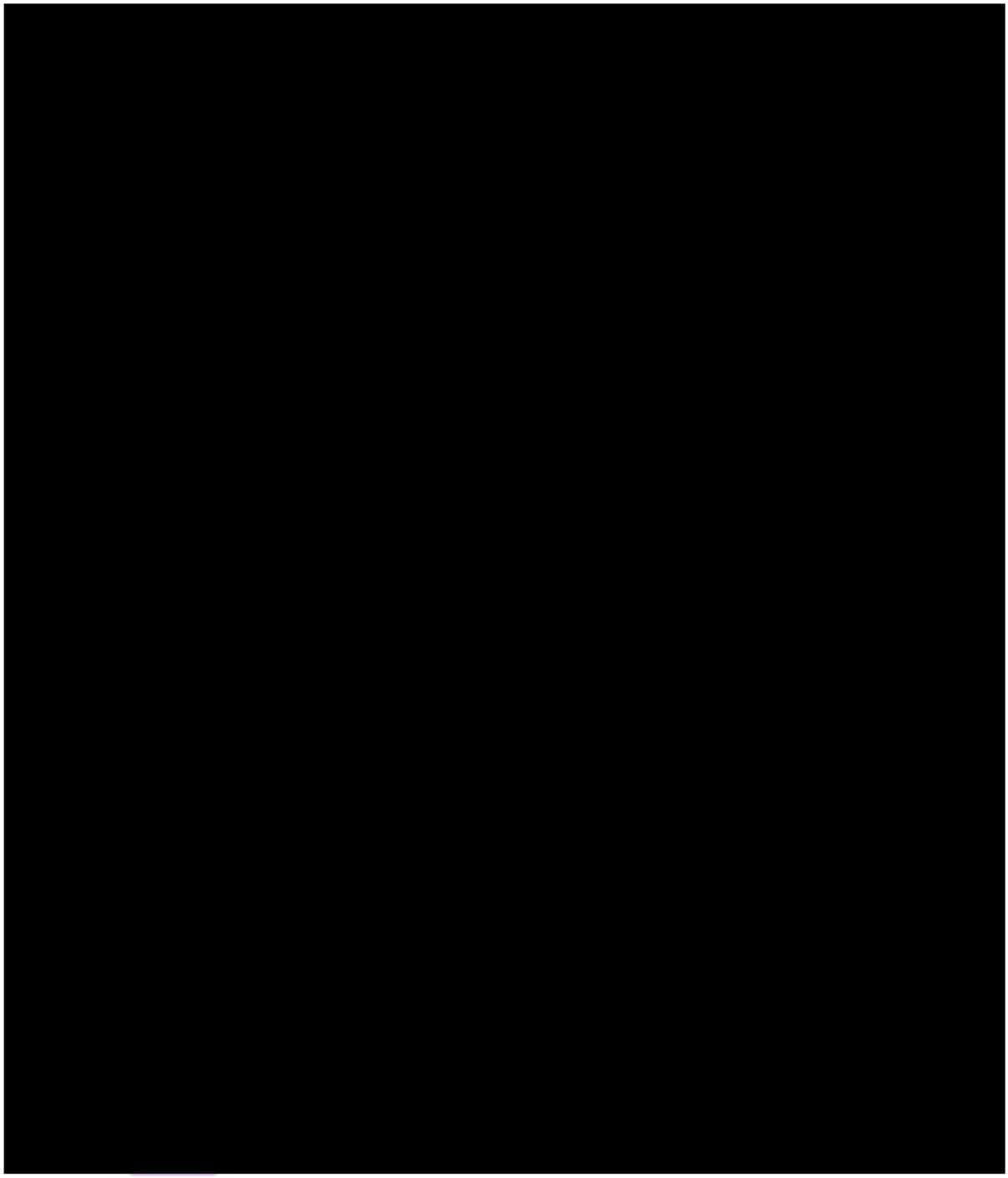

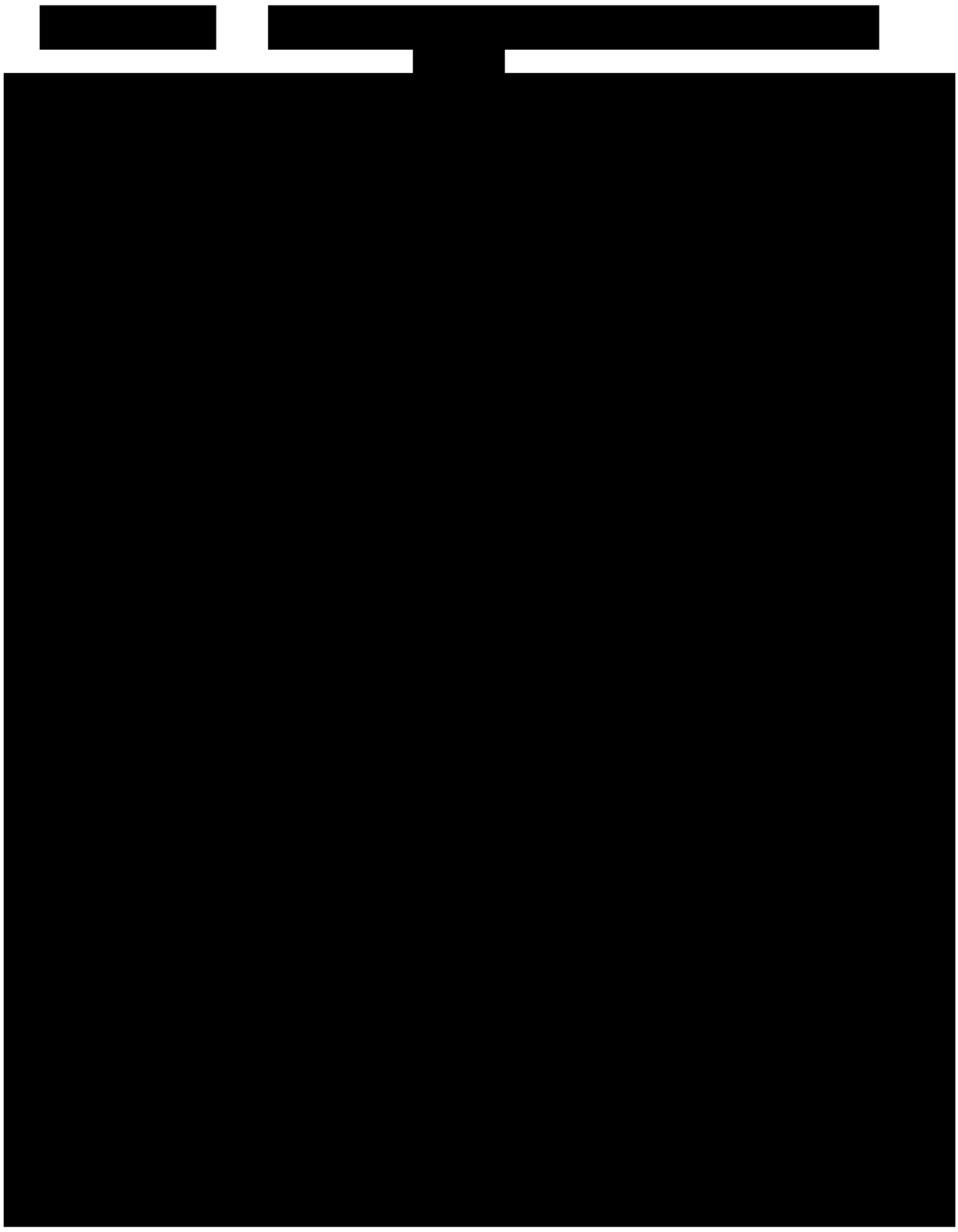

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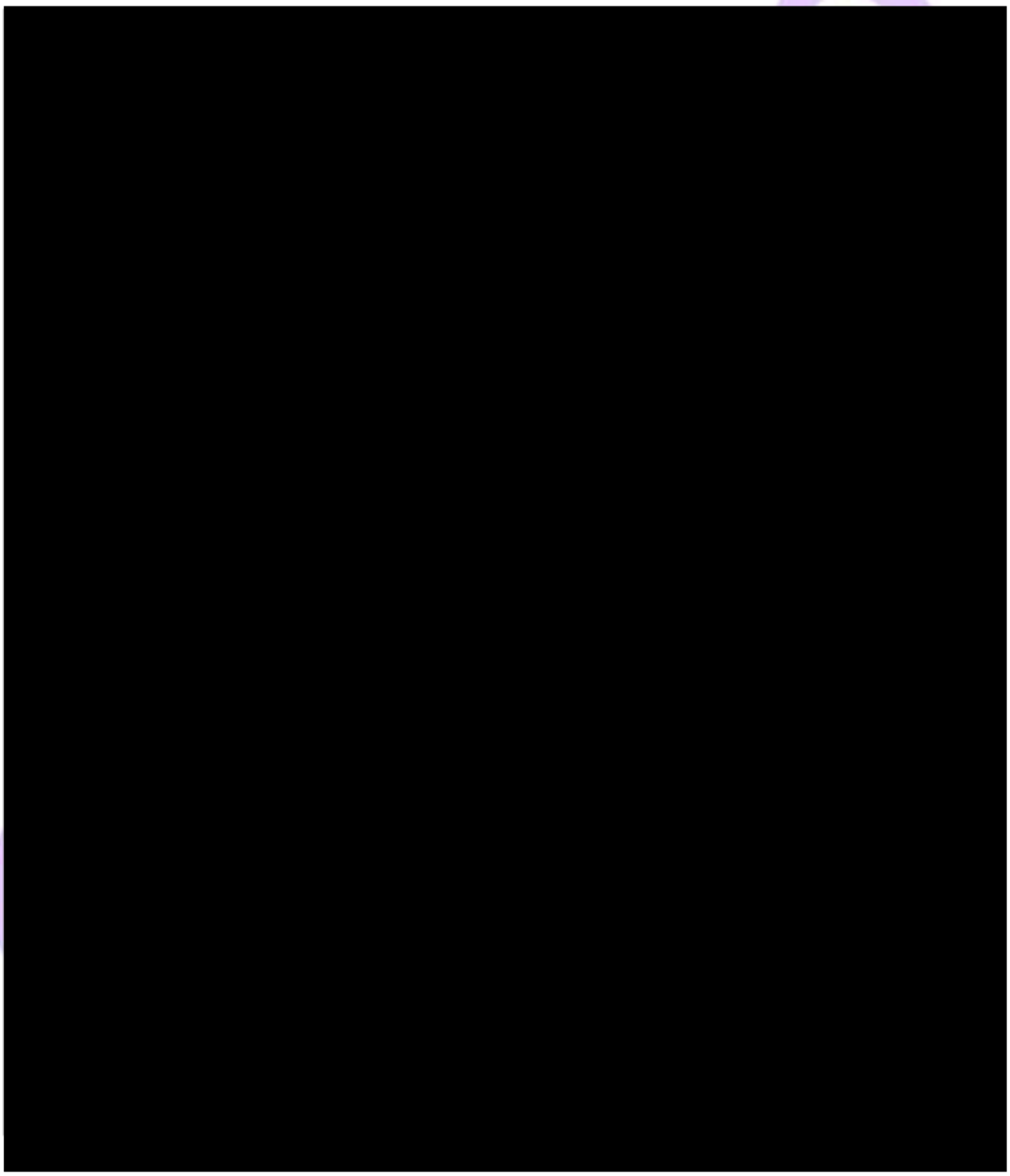

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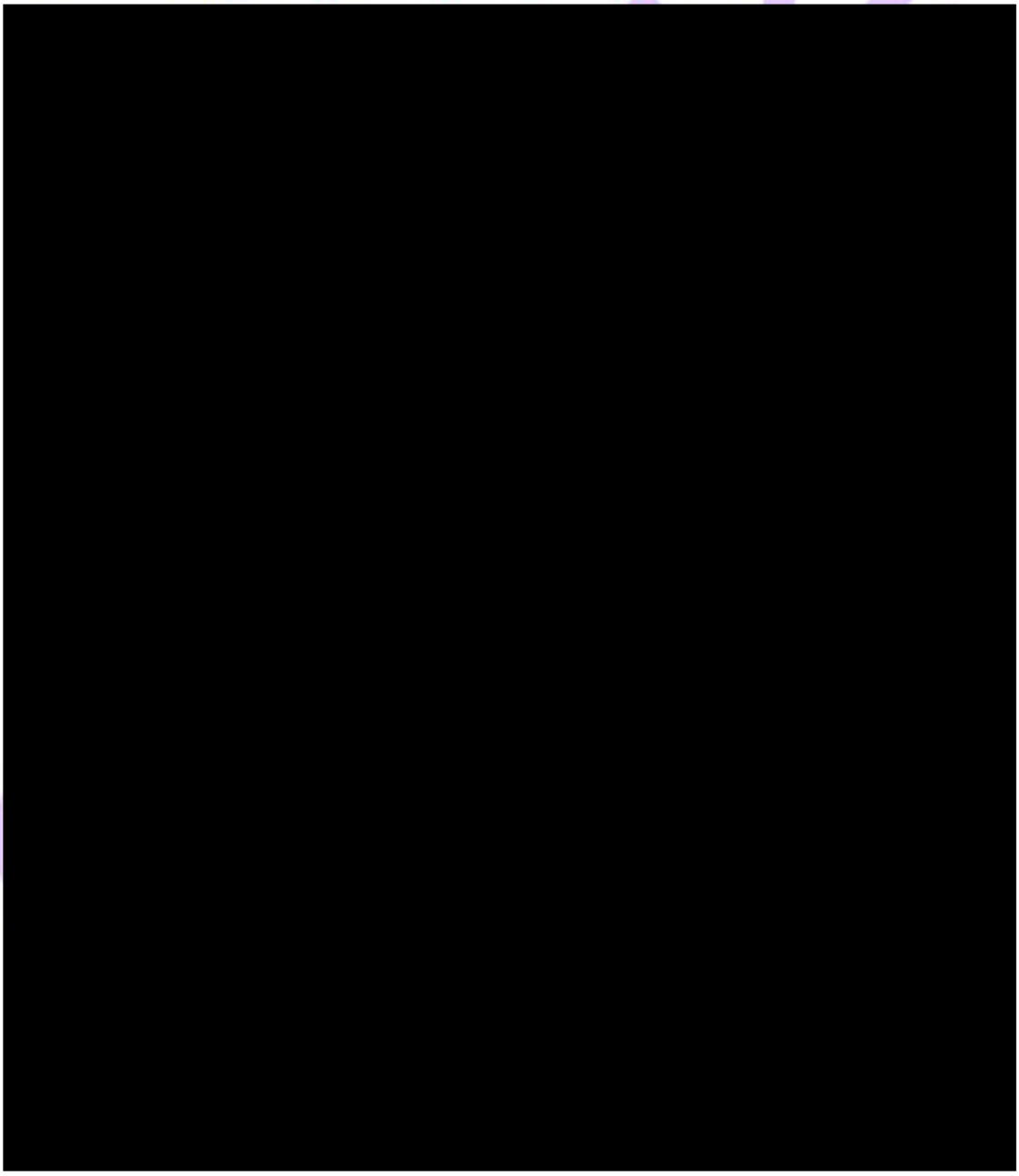

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