Clinical trial results:
Phase III, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy (Induction of Remission) and Safety of Etrolizumab Compared With Adalimumab and Placebo in Patients With Moderate to Severe Ulcerative Colitis who are Naive to TNF Inhibitors

Summary

EudraCT number	2013-004277-27
Trial protocol	LV LT HR BG GR HU CZ
Global end of trial date	25 May 2020

Results information

Result version number	v1
This version publication date	27 February 2021
First version publication date	27 February 2021

Trial information

Trial identification

Sponsor protocol code	GA28949

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02171429
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche, Ltd.
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche, Ltd., F. Hoffmann-La Roche, Ltd., 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche, Ltd., F. Hoffmann-La Roche, Ltd., 41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 March 2020
Global end of trial reached?	Yes
Global end of trial date	25 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

-To evaluate the efficacy of etrolizumab (105 mg SC every 4 weeks [Q4W]) compared with placebo for the induction of remission in TNF-naive patients with ulcerative colitis as determined by the Mayo Clinic Score at Week 10

Protection of trial subjects:

This study was conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever afforded the greater protection to the individual. All subjects signed an informed consent form before participating in the study.

Background therapy:

During the induction phase (Day 1 to Week 10), continuation of stable baseline doses of the following non-investigational medicinal products were permitted: oral 5-aminosalicylic acid (5-ASA); azathioprine; 6-mercaptopurine; methotrexate; corticosteroids up to 30 milligrams per day (mg/day) of prednisone (or equivalent); and budesonide up to 9 mg/day. From Week 10 to Week 14, subjects who achieved clinical remission at Week 10 were to continue immunosuppressants (AZA, 6-MP, MTX) at a stable dose unless dose reduction or discontinuation was required due to immunosuppressant-related toxicity. For subjects who stayed in the study, corticosteroids were to be tapered starting from Week 10 in those who achieved clinical remission. Throughout the study, probiotics and oral 5-ASA may have been continued at a stable dose. Occasional use of NSAIDs and acetaminophen (e.g., for headache, arthritis, myalgias, menstrual cramps) and aspirin up to 325 mg daily were permitted throughout the study. Antidiarrheals (e.g., loperamide, diphenoxylate with atropine) for control of chronic diarrhea were permitted throughout the study.

Evidence for comparator: -

Actual start date of recruitment	14 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Bulgaria: 24
Country: Number of subjects enrolled	Brazil: 23
Country: Number of subjects enrolled	Colombia: 4
Country: Number of subjects enrolled	Czechia: 13
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Lithuania: 16

Country: Number of subjects enrolled	Latvia: 9
Country: Number of subjects enrolled	Malaysia: 7
Country: Number of subjects enrolled	New Zealand: 21
Country: Number of subjects enrolled	Poland: 57
Country: Number of subjects enrolled	Russian Federation: 68
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	Ukraine: 76
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	358
EEA total number of subjects	125

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	344
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects on concomitant background therapy were allowed to continue receiving stable baseline doses of the following non-investigational medicinal products during the study: oral 5-ASA; azathioprine; 6-mercaptopurine; methotrexate; corticosteroids up to 30 mg/day of prednisone (or equivalent); and/or budesonide up to 9 mg/day.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

The double-blinded treatment period consisted of a 10-week induction period and an additional 4-week treatment period for participants who met the definition of clinical remission at Week 10. Participants with moderate-to-severe ulcerative colitis who were naive to TNF inhibitors were randomized to this arm to receive placebo matching to etrolizumab subcutaneously (SC) once every 4 weeks (Q4W) up to Week 12 (at Weeks 0 [Day 1], 4, 8, and 12 [clinical remitters only]) and placebo matching to adalimumab SC once every 2 weeks (Q2W) up to Week 8 (at Weeks 0 [Day 1], 2, 4, 6, and 8).

Arm type	Placebo
Investigational medicinal product name	Etrolizumab Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

The placebo matching to etrolizumab was supplied in a pre-filled syringe and was administered as an SC injection once every 4 weeks up to Week 12 (at Weeks 0 [Day 1], 4, 8, and 12 [clinical remitters only]).

Investigational medicinal product name	Adalimumab Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

The placebo matching to adalimumab was supplied in a pre-filled syringe and was administered as an SC injection once every 2 weeks (Q2W) up to Week 8 (at Weeks 0 [Day 1], 2, 4, 6, and 8).

Arm title	Adalimumab

Arm description:

The double-blinded treatment period consisted of a 10-week induction period and an additional 4-week treatment period for participants who met the definition of clinical remission at Week 10. Participants with moderate-to-severe ulcerative colitis who were naive to TNF inhibitors were randomized to this arm to receive adalimumab subcutaneously (SC) Q2W up to Week 8 (160 mg at Week 0 [Day 1], 80 mg at Week 2, 40 mg at Weeks 4, 6, and 8) and placebo matching to etrolizumab SC Q4W up to Week 12 (at Weeks 0 [Day 1], 4, 8, and 12 [clinical remitters only]).

Arm type	Active comparator

Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	Humira
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Adalimumab was supplied in a pre-filled syringe and was administered as an SC injection once every 2 weeks (Q2W) up to Week 8 (at Weeks 0 [Day 1], 2, 4, 6, and 8). Adalimumab was to be administered at a dose of 160 milligrams (mg) at Week 0 (Day 1; 4 injections), 80 mg at Week 2 (2 injections), and 40 mg (1 injection) at Weeks 4, 6, and 8.

Investigational medicinal product name	Etrolizumab Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

The placebo matching to etrolizumab was supplied in a pre-filled syringe and was administered as an SC injection once every 4 weeks up to Week 12 (at Weeks 0 [Day 1], 4, 8, and 12 [clinical remitters only]).

Arm title	Etrolizumab

Arm description:

The double-blinded treatment period consisted of a 10-week induction period and an additional 4-week treatment period for participants who met the definition of clinical remission at Week 10. Participants with moderate-to-severe ulcerative colitis who were naive to TNF inhibitors were randomized to this arm to receive etrolizumab 105 mg subcutaneously (SC) Q4W up to Week 12 (at Weeks 0 [Day 1], 4, 8, and 12 [clinical remitters only]) and placebo matching to adalimumab SC Q2W up to Week 8 (at Weeks 0 [Day 1], 2, 4, 6, and 8).

Arm type	Experimental
Investigational medicinal product name	Etrolizumab
Investigational medicinal product code	RO5490261
Other name	PRO145223
Pharmaceutical forms	Solution for injection in pre-filled pen, Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Etrolizumab was supplied in a pre-filled syringe and was administered as an SC injection at a dose of 105 mg once every 4 weeks up to Week 12 (at Weeks 0 [Day 1], 4, 8, and 12 [clinical remitters only]).

Investigational medicinal product name	Adalimumab Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

The placebo matching to adalimumab was supplied in a pre-filled syringe and was administered as an SC injection once every 2 weeks (Q2W) up to Week 8 (at Weeks 0 [Day 1], 2, 4, 6, and 8).

Number of subjects in period 1	Placebo	Adalimumab	Etrolizumab
Started	72	143	143
Completed Week 10 Visit	70 [1]	141	141
Completed	71	140	138
Not completed	1	3	5

Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	1	1	1
Non-Compliance	-	-	1
Physician decision	-	-	1
Not Specified	-	1	1
Lost to follow-up	-	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants who did not complete the Week 10 visit could have subsequently completed the study if they either rolled into the open-label extension study or completed the 12 weeks of safety follow-up after early treatment discontinuation.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

Reporting group description:

The double-blinded treatment period consisted of a 10-week induction period and an additional 4-week treatment period for participants who met the definition of clinical remission at Week 10. Participants with moderate-to-severe ulcerative colitis who were naive to TNF inhibitors were randomized to this arm to receive placebo matching to etrolizumab subcutaneously (SC) once every 4 weeks (Q4W) up to Week 12 (at Weeks 0 [Day 1], 4, 8, and 12 [clinical remitters only]) and placebo matching to adalimumab SC once every 2 weeks (Q2W) up to Week 8 (at Weeks 0 [Day 1], 2, 4, 6, and 8).

Reporting group title	Adalimumab

Reporting group description:

The double-blinded treatment period consisted of a 10-week induction period and an additional 4-week treatment period for participants who met the definition of clinical remission at Week 10. Participants with moderate-to-severe ulcerative colitis who were naive to TNF inhibitors were randomized to this arm to receive adalimumab subcutaneously (SC) Q2W up to Week 8 (160 mg at Week 0 [Day 1], 80 mg at Week 2, 40 mg at Weeks 4, 6, and 8) and placebo matching to etrolizumab SC Q4W up to Week 12 (at Weeks 0 [Day 1], 4, 8, and 12 [clinical remitters only]).

Reporting group title	Etrolizumab

Reporting group description:

The double-blinded treatment period consisted of a 10-week induction period and an additional 4-week treatment period for participants who met the definition of clinical remission at Week 10. Participants with moderate-to-severe ulcerative colitis who were naive to TNF inhibitors were randomized to this arm to receive etrolizumab 105 mg subcutaneously (SC) Q4W up to Week 12 (at Weeks 0 [Day 1], 4, 8, and 12 [clinical remitters only]) and placebo matching to adalimumab SC Q2W up to Week 8 (at Weeks 0 [Day 1], 2, 4, 6, and 8).

Reporting group values	Placebo	Adalimumab	Etrolizumab
Number of subjects	72	143	143
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	70	139	135
From 65-84 years	2	4	8
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	40.3	39.7	41.1
standard deviation	± 12.5	± 12.6	± 14.4
Sex: Female, Male Units: Participants			
Female	34	62	59
Male	38	81	84

Race/Ethnicity, Customized Units: Subjects			
Asian	4	4	4
Black or African American	1	4	1
White	65	131	133
Other	2	4	5
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	11	12
Not Hispanic or Latino	67	130	128
Unknown or Not Reported	0	2	3
Disease Location Units: Subjects			
Left-Sided Colitis	48	86	86
Extensive Colitis	7	13	11
Pancolitis	17	44	46
Mayo Clinic Score (MCS) ≤9 or ≥10 at Baseline			
Participants were stratified by concomitant treatment with corticosteroids (yes/no) at randomization, concomitant treatment with immunosuppressants (yes/no) at randomization, and disease activity measured during screening (MCS ≤9/MCS ≥10). The MCS ranges from 0 to 12 and is a composite of the four following assessments of disease activity: stool frequency subscore, rectal bleeding subscore, endoscopy subscore, and physician's global assessment (PGA) subscore. Each of the four assessments was rated with a score from 0 to 3, with higher scores indicating more severe disease.			
Units: Subjects			
MCS ≤9	46	96	96
MCS ≥10	26	47	47
Baseline Treatment: None, Corticosteroids (CS) or Immunosuppressants (IS) Alone, or Both CS and IS			
Participants were stratified by concomitant treatment with corticosteroids (yes/no) at randomization, concomitant treatment with immunosuppressants (yes/no) at randomization, and disease activity measured during screening (MCS ≤9/MCS ≥10).			
Units: Subjects			
None	27	53	55
Corticosteroids (CS) Alone	23	42	40
Immunosuppressants (IS) Alone	14	28	28
Both CS and IS	8	20	20
Nancy Histological Index (NHI) Score of ≤1 or >1, or Missing, at Baseline			
Histologic disease activity was measured using the Nancy Histological Index (NHI) score, ranging from 0 to 4, with the following definitions for each grade: 0 is no histologically significant disease; 1 is chronic inflammatory infiltrate with no acute inflammatory infiltrate; and 2, 3, and 4 are mildly, moderately, and severely active disease, respectively.			
Units: Subjects			
NHI Score ≤1	9	23	21
NHI Score >1	62	114	108
Missing	1	6	14

Reporting group values	Total		
Number of subjects	358		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	344		
From 65-84 years	14		
85 years and over	0		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Participants			
Female	155		
Male	203		
Race/Ethnicity, Customized			
Units: Subjects			
Asian	12		
Black or African American	6		
White	329		
Other	11		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	28		
Not Hispanic or Latino	325		
Unknown or Not Reported	5		
Disease Location			
Units: Subjects			
Left-Sided Colitis	220		
Extensive Colitis	31		
Pancolitis	107		
Mayo Clinic Score (MCS) ≤9 or ≥10 at Baseline			
Participants were stratified by concomitant treatment with corticosteroids (yes/no) at randomization, concomitant treatment with immunosuppressants (yes/no) at randomization, and disease activity measured during screening (MCS ≤9/MCS ≥10). The MCS ranges from 0 to 12 and is a composite of the four following assessments of disease activity: stool frequency subscore, rectal bleeding subscore, endoscopy subscore, and physician's global assessment (PGA) subscore. Each of the four assessments was rated with a score from 0 to 3, with higher scores indicating more severe disease.			
Units: Subjects			
MCS ≤9	238		
MCS ≥10	120		
Baseline Treatment: None, Corticosteroids (CS) or Immunosuppressants (IS) Alone, or Both CS and IS			
Participants were stratified by concomitant treatment with corticosteroids (yes/no) at randomization, concomitant treatment with immunosuppressants (yes/no) at randomization, and disease activity measured during screening (MCS ≤9/MCS ≥10).			
Units: Subjects			
None	135		
Corticosteroids (CS) Alone	105		

Immunosuppressants (IS) Alone	70		
Both CS and IS	48		
Nancy Histological Index (NHI) Score of ≤1 or >1, or Missing, at Baseline			
Histologic disease activity was measured using the Nancy Histological Index (NHI) score, ranging from 0 to 4, with the following definitions for each grade: 0 is no histologically significant disease; 1 is chronic inflammatory infiltrate with no acute inflammatory infiltrate; and 2, 3, and 4 are mildly, moderately, and severely active disease, respectively.			
Units: Subjects			
NHI Score ≤1	53		
NHI Score >1	284		
Missing	21		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

The double-blinded treatment period consisted of a 10-week induction period and an additional 4-week treatment period for participants who met the definition of clinical remission at Week 10. Participants with moderate-to-severe ulcerative colitis who were naive to TNF inhibitors were randomized to this arm to receive placebo matching to etrolizumab subcutaneously (SC) once every 4 weeks (Q4W) up to Week 12 (at Weeks 0 [Day 1], 4, 8, and 12 [clinical remitters only]) and placebo matching to adalimumab SC once every 2 weeks (Q2W) up to Week 8 (at Weeks 0 [Day 1], 2, 4, 6, and 8).

Reporting group title	Adalimumab

Reporting group description:

The double-blinded treatment period consisted of a 10-week induction period and an additional 4-week treatment period for participants who met the definition of clinical remission at Week 10. Participants with moderate-to-severe ulcerative colitis who were naive to TNF inhibitors were randomized to this arm to receive adalimumab subcutaneously (SC) Q2W up to Week 8 (160 mg at Week 0 [Day 1], 80 mg at Week 2, 40 mg at Weeks 4, 6, and 8) and placebo matching to etrolizumab SC Q4W up to Week 12 (at Weeks 0 [Day 1], 4, 8, and 12 [clinical remitters only]).

Reporting group title	Etrolizumab

Reporting group description:

The double-blinded treatment period consisted of a 10-week induction period and an additional 4-week treatment period for participants who met the definition of clinical remission at Week 10. Participants with moderate-to-severe ulcerative colitis who were naive to TNF inhibitors were randomized to this arm to receive etrolizumab 105 mg subcutaneously (SC) Q4W up to Week 12 (at Weeks 0 [Day 1], 4, 8, and 12 [clinical remitters only]) and placebo matching to adalimumab SC Q2W up to Week 8 (at Weeks 0 [Day 1], 2, 4, 6, and 8).

Primary: Percentage of Participants in Remission With Etrolizumab Compared With Placebo at Week 10, as Determined by the Mayo Clinic Score (MCS)

End point title	Percentage of Participants in Remission With Etrolizumab Compared With Placebo at Week 10, as Determined by the Mayo Clinic Score (MCS)[1]

End point description:

The Mayo Clinic Score (MCS) ranges from 0 to 12 and is a composite of the four following assessments of disease activity: stool frequency subscore, rectal bleeding subscore, endoscopy subscore, and physician's global assessment (PGA) subscore. Each of the four assessments was rated with a score from 0 to 3, with higher scores indicating more severe disease. Remission was defined as MCS less than or equal to (≤)2 with individual subscores ≤1 and a rectal bleeding subscore of 0. Participants were also classified as non-remitters if Week 10 assessments were missing or if they had received permitted/prohibited rescue therapy prior to assessment. Participants were stratified by concomitant treatment with corticosteroids or immunosuppressants at randomization and disease activity measured during screening (MCS ≤9/MCS ≥10); the Cochran-Mantel-Haenszel test adjusted the difference in remission rates and associated 95% confidence interval for the stratification factors.

End point type	Primary

End point timeframe:

Week 10

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary outcome measure only compared remission rates between the etrolizumab and placebo arms.

End point values	Placebo	Etrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	143		
Units: Percentage of participants				
number (confidence interval 95%)	11.1 (5.74 to 20.42)	18.2 (12.72 to 25.31)		

Statistical analyses

Statistical analysis title	Etrolizumab vs. Placebo: Remission at Week 10

Statistical analysis description:

The null hypothesis (H0): the percentage of participants achieving remission at Week 10 was the same in both the placebo and etrolizumab arms. The alternative hypothesis (H1): the percentage of participants achieving remission at Week 10 was not the same in the placebo and etrolizumab arms.

Comparison groups	Placebo v Etrolizumab
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1729 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Remission Rates
Point estimate	7.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.83
upper limit	16.12

Notes:

[2] - The threshold for statistical significance was a p-value <0.05.

Secondary: Percentage of Participants in Remission With Etrolizumab Compared With Adalimumab at Week 10, as Determined by the MCS

End point title	Percentage of Participants in Remission With Etrolizumab Compared With Adalimumab at Week 10, as Determined by the MCS[3]

End point description:

The Mayo Clinic Score (MCS) ranges from 0 to 12 and is a composite of the four following assessments of disease activity: stool frequency subscore, rectal bleeding subscore, endoscopy subscore, and physician's global assessment (PGA) subscore. Each of the four assessments was rated with a score from 0 to 3, with higher scores indicating more severe disease. Remission was defined as MCS less than or equal to (≤)2 with individual subscores ≤1 and a rectal bleeding subscore of 0. Participants were also classified as non-remitters if Week 10 assessments were missing or if they had received permitted/prohibited rescue therapy prior to assessment. Participants were stratified by concomitant treatment with corticosteroids or immunosuppressants at randomization and disease activity measured during screening (MCS ≤9/MCS ≥10). The Cochran-Mantel-Haenszel test adjusted the difference in remission rates and associated 95% confidence interval for the stratification factors.

End point type	Secondary

End point timeframe:

Week 10

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This secondary outcome measure only compared remission rates between the etrolizumab

and adalimumab arms.

End point values	Adalimumab	Etrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	143		
Units: Percentage of participants				
number (confidence interval 95%)	24.5 (18.16 to 32.13)	18.2 (12.72 to 25.31)		

Statistical analyses

Statistical analysis title	Etrolizumab vs. Adalimumab: Remission at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details. Individual study results are shown, however, this endpoint was formally tested using pooled study data from this study and an identically designed study (GA28948); those pooled results cannot be provided on the registry due to its limitations.

Comparison groups	Adalimumab v Etrolizumab
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1458 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Remission Rates
Point estimate	-6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.26
upper limit	2.73

Notes:

[4] - Nominal p-value; it has not been adjusted for multiplicity.

Secondary: Percentage of Participants in Clinical Remission at Week 10, as Determined by the MCS

End point title	Percentage of Participants in Clinical Remission at Week 10, as Determined by the MCS

End point description:

The Mayo Clinic Score (MCS) ranges from 0 to 12 and is a composite of the four following assessments of disease activity: stool frequency subscore, rectal bleeding subscore, endoscopy subscore, and physician's global assessment (PGA) subscore. Each of the four assessments was rated with a score from 0 to 3, with higher scores indicating more severe disease. Clinical remission was defined as MCS less than or equal to (≤)2 with individual subscores ≤1. Participants were also classified as non-remitters if Week 10 assessments were missing or if they had received permitted/prohibited rescue therapy prior to assessment. Participants were stratified by concomitant treatment with corticosteroids or immunosuppressants at randomization and disease activity measured during screening (MCS ≤9/MCS ≥10). The Cochran-Mantel-Haenszel test adjusted the differences in remission rates and associated 95% confidence intervals for the stratification factors.

End point type	Secondary

End point timeframe:

Week 10

End point values	Placebo	Adalimumab	Etrolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	143	143	
Units: Percentage of participants				
number (confidence interval 95%)	11.1 (5.74 to 20.42)	25.9 (19.39 to 33.62)	18.9 (13.31 to 26.08)	

Statistical analyses

Statistical analysis title	Etro vs. Placebo: Clinical Remission at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details.

Comparison groups	Placebo v Etrolizumab
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1382 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Remission Rates
Point estimate	7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.19
upper limit	16.87

Notes:

[5] - Nominal p-value; it has not been adjusted for multiplicity.

Statistical analysis title	Etro vs. Adalimumab: Clinical Remission at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details.

Comparison groups	Adalimumab v Etrolizumab
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1163 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Remission Rates
Point estimate	-7.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.1
upper limit	2.22

Notes:

[6] - Nominal p-value; it has not been adjusted for multiplicity.

Secondary: Percentage of Participants With Clinical Response at Week 10, as Determined by the MCS

End point title	Percentage of Participants With Clinical Response at Week 10, as Determined by the MCS

End point description:

The Mayo Clinic Score (MCS) ranges from 0 to 12 and is a composite of the four following assessments of disease activity: stool frequency subscore, rectal bleeding subscore, endoscopy subscore, and physician's global assessment subscore. Each of the four assessments was rated with a score from 0 to 3, with higher scores indicating more severe disease. Clinical Response was defined as: MCS ≥3-point decrease and 30% reduction from baseline as well as ≥1-point decrease in rectal bleeding subscore or an absolute rectal bleeding score of 0 or 1. Non-responders also included participants with missing Week 10 assessments or those who had received permitted/prohibited rescue therapy prior to assessment. Participants were stratified by concomitant treatment with corticosteroids or immunosuppressants at randomization and disease activity measured during screening (MCS ≤9 or ≥10); the CMH test adjusted the differences in response rates and associated 95% CIs for the stratification factors.

End point type	Secondary

End point timeframe:

Week 10

End point values	Placebo	Adalimumab	Etrolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	143	143	
Units: Percentage of participants				
number (confidence interval 95%)	38.9 (28.47 to 50.44)	54.5 (46.37 to 62.48)	52.4 (44.31 to 60.46)	

Statistical analyses

Statistical analysis title	Etro vs. Placebo: Clinical Response at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details.

Comparison groups	Placebo v Etrolizumab
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1729 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	14

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	27.19

Notes:

[7] - p-value has been adjusted for multiplicity.

Statistical analysis title	Etro vs. Adalimumab: Clinical Response at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details. Individual study results are shown, however, this endpoint was formally tested using pooled study data from this study and an identically designed study (GA28948); those pooled results cannot be provided on the registry due to its limitations.

Comparison groups	Adalimumab v Etrolizumab
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6726 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.83
upper limit	9.01

Notes:

[8] - Nominal p-value; it has not been adjusted for multiplicity.

Secondary: Percentage of Participants With Improvement in Endoscopic Appearance of the Mucosa at Week 10, as Determined by the Mayo Endoscopy Subscore

End point title	Percentage of Participants With Improvement in Endoscopic Appearance of the Mucosa at Week 10, as Determined by the Mayo Endoscopy Subscore

End point description:

Improvement in endoscopic appearance of the mucosa was defined as a Mayo Clinic Score (MCS) endoscopy subscore ≤1. Blinded gastroenterologists experienced in inflammatory bowel disease performed central reading of endoscopies at an independent review facility. The rectum, sigmoid, and descending colon segments were assessed and each segment was assigned a score of 0 to 3, with higher scores indicating more severe disease. At baseline all segments were reviewed and the worst score from the three segments was recorded as the endoscopy subscore. Post-baseline the endoscopy score was the worst score of all segments that had been assessed at baseline, if the baseline endoscopy score had a sigmoid colon score ≤1. If at baseline the sigmoid colon score was ≥2, the post-baseline endoscopy score was the sigmoid colon score value. Non-responders also included participants with missing Week 10 assessments or those who had received permitted/prohibited rescue therapy prior to assessment.

End point type	Secondary

End point timeframe:

Week 10

End point values	Placebo	Adalimumab	Etrolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	143	143	
Units: Percentage of participants				
number (confidence interval 95%)	30.6 (21.13 to 41.95)	42.7 (34.85 to 50.85)	39.9 (32.20 to 48.05)	

Statistical analyses

Statistical analysis title	Etro vs. Placebo: Endoscopic Appearance at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details.

Comparison groups	Placebo v Etrolizumab
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2372 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	9.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.31
upper limit	21.95

Notes:

[9] - p-value has been adjusted for multiplicity.

Statistical analysis title	Etro vs. Ada.: Endoscopic Appearance at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details. Individual study results are shown, however, this endpoint was formally tested using pooled study data from this study and an identically designed study (GA28948); those pooled results cannot be provided on the registry due to its limitations.

Comparison groups	Adalimumab v Etrolizumab
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5341 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.76
upper limit	7.82

Notes:

[10] - Nominal p-value; it has not been adjusted for multiplicity.

Secondary: Percentage of Participants in Endoscopic Remission at Week 10, as Determined by the MCS Endoscopy Subscore

End point title	Percentage of Participants in Endoscopic Remission at Week 10, as Determined by the MCS Endoscopy Subscore

End point description:

Endoscopic remission was defined as a Mayo Clinic Score (MCS) endoscopy subscore of 0. Blinded gastroenterologists experienced in inflammatory bowel disease performed central reading of endoscopies at an independent review facility. The rectum, sigmoid, and descending colon segments were assessed and each segment was assigned a score of 0 to 3, with higher scores indicating more severe disease. At baseline all segments were reviewed and the worst score from the three segments was recorded as the endoscopy subscore. Post-baseline the endoscopy score was the worst score of all segments that had been assessed at baseline, if the baseline endoscopy score had a sigmoid colon score ≤1. If at baseline the sigmoid colon score was ≥2, the post-baseline endoscopy score was the sigmoid colon score value. Non-responders also included participants with missing Week 10 assessments or those who had received permitted/prohibited rescue therapy prior to assessment.

End point type	Secondary

End point timeframe:

Week 10

End point values	Placebo	Adalimumab	Etrolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	143	143	
Units: Percentage of participants				
number (confidence interval 95%)	8.3 (3.88 to 17.01)	26.6 (20.02 to 34.36)	19.6 (13.91 to 26.84)	

Statistical analyses

Statistical analysis title	Etro vs. Placebo: Endoscopic Remission at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details.

Comparison groups	Placebo v Etrolizumab
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2372 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Remission Rates
Point estimate	11.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	19.76

Notes:

[11] - p-value has been adjusted for multiplicity.

Statistical analysis title	Etro vs. Ada.: Endoscopic Remission at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details. Individual study results are shown, however, this endpoint was formally tested using pooled study data from this study and an identically designed study (GA28948); those pooled results cannot be provided on the registry due to its limitations.

Comparison groups	Adalimumab v Etrolizumab
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1192 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Remission Rates
Point estimate	-7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.2
upper limit	2.33

Notes:

[12] - Nominal p-value; it has not been adjusted for multiplicity.

Secondary: Percentage of Participants in Remission at Week 10 and Week 14, as Determined by the MCS

End point title	Percentage of Participants in Remission at Week 10 and Week 14, as Determined by the MCS

End point description:

The Mayo Clinic Score (MCS) ranges from 0 to 12 and is a composite of the four following assessments of disease activity: stool frequency subscore, rectal bleeding subscore, endoscopy subscore, and physician's global assessment (PGA) subscore. Each of the four assessments was rated with a score from 0 to 3, with higher scores indicating more severe disease. Remission was defined as MCS less than or equal to (≤)2 with individual subscores ≤1 and a rectal bleeding subscore of 0. Participants were also classified as non-remitters if Week 10 or 14 assessments were missing or the participant received permitted/prohibited rescue therapy prior to assessment. Participants were stratified by concomitant treatment with corticosteroids or immunosuppressants at randomization and disease activity measured during screening (MCS ≤9/MCS ≥10). The Cochran-Mantel-Haenszel test adjusted the differences in remission rates and associated 95% confidence intervals for the stratification factors.

End point type	Secondary

End point timeframe:

Week 10 and 14

End point values	Placebo	Adalimumab	Etrolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	143	143	
Units: Percentage of participants				
number (confidence interval 95%)	6.9 (3.00 to 15.25)	14.7 (9.81 to 21.41)	9.8 (5.92 to 15.76)	

Statistical analyses

Statistical analysis title	Etro vs. Placebo: Remission at Weeks 10 and 14

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details.

Comparison groups	Placebo v Etrolizumab
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4772 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Remission Rates
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.47
upper limit	10.14

Notes:

[13] - Nominal p-value; it has not been adjusted for multiplicity.

Statistical analysis title	Etro vs. Ada.: Remission at Weeks 10 and 14

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details.

Comparison groups	Adalimumab v Etrolizumab
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1801 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Remission Rates
Point estimate	-5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.95
upper limit	2.63

Notes:

[14] - Nominal p-value; it has not been adjusted for multiplicity.

Secondary: Percentage of Participants With Histologic Remission at Week 10, as

Determined by the Nancy Histological Index

End point title	Percentage of Participants With Histologic Remission at Week 10, as Determined by the Nancy Histological Index

End point description:

Histologic remission is defined by the resolution of neutrophilic inflammation (e.g., absence of neutrophils in the crypts and lamina propria), defined by a Nancy Histological Index (NHI) score of ≤1. The NHI score ranges from 0 to 4, with the following definitions for each grade: 0 is no histologically significant disease; 1 is chronic inflammatory infiltrate with no acute inflammatory infiltrate; and 2, 3, and 4 are mildly, moderately, and severely active disease, respectively. A small pool of central readers who were blinded to both treatment arm and timepoint performed the histologic scoring. The same reader scored all slides for a given participant based on biopsies from the most inflamed region of the sigmoid colon. Participants were also classified as non-remitters if Week 10 assessments were missing or if they had received rescue therapy prior to assessment. The Cochran-Mantel-Haenszel test adjusted the difference in remission rates and 95% CI for the stratification factors.

End point type	Secondary

End point timeframe:

Week 10

End point values	Placebo	Adalimumab	Etrolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62[15]	114[16]	108[17]	
Units: Percentage of participants				
number (confidence interval 95%)	21.0 (12.68 to 32.64)	43.9 (35.10 to 53.02)	30.6 (22.66 to 39.79)	

Notes:

[15] - Subjects analyzed only includes those with NHI score >1 at baseline.

[16] - Subjects analyzed only includes those with NHI score >1 at baseline.

[17] - Subjects analyzed only includes those with NHI score >1 at baseline.

Statistical analyses

Statistical analysis title	Etro vs. Placebo: Histologic Remission at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details.

Comparison groups	Placebo v Etrolizumab
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2729 [18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Remission Rates
Point estimate	9.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.71
upper limit	22.02

Notes:

[18] - p-value has been adjusted for multiplicity.

Statistical analysis title	Etro vs. Ada.: Histologic Remission at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details. Individual study results are shown, however, this endpoint was formally tested using pooled study data from this study and an identically designed study (GA28948); those pooled results cannot be provided on the registry due to its limitations.

Comparison groups	Adalimumab v Etrolizumab
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0215 [19]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Remission Rates
Point estimate	-14.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.97
upper limit	-2.04

Notes:

[19] - Nominal p-value; it has not been adjusted for multiplicity.

Secondary: Change From Baseline in MCS Rectal Bleeding Subscore at Week 6

End point title	Change From Baseline in MCS Rectal Bleeding Subscore at Week 6

End point description:

Rectal bleeding data were collected via the participant's diaries and each day a participant provided a score from 0 to 3 according to the following definitions: 0 = no blood in the stool; 1 = streaks of blood with stool less than half the time; 2 = obvious blood with stool most of the time; 3 = blood alone passed. The Mayo Clinic Score (MCS) rectal bleeding subscore was calculated as the worst value of three days of daily diary scores closest to anchor dates at baseline and post-baseline. The data was considered non-parametric and was reported using RANK analysis of covariance (ANCOVA). Participants were stratified by concomitant treatment with corticosteroids or immunosuppressants at randomization and disease activity measured during screening (MCS ≤9/MCS ≥10); the model adjusted for these stratification factors along with the baseline rectal bleeding (RB) subscore.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	Placebo	Adalimumab	Etrolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	143	143	
Units: Score on a scale				
median (inter-quartile range (Q1-Q3))	0.0 (-1.0 to 0.0)	-1.0 (-2.0 to 0.0)	-1.0 (-2.0 to 0.0)	

Statistical analyses

Statistical analysis title	Etro vs. Placebo: MCS Rectal Bleeding at Week 6

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details.

Comparison groups	Placebo v Etrolizumab
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1729 [20]
Method	Rank ANCOVA

Notes:

[20] - p-value has been adjusted for multiplicity.

Statistical analysis title	Etro vs. Ada.: MCS Rectal Bleeding at Week 6

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details. Individual study results are shown, however, this endpoint was formally tested using pooled study data from this study and an identically designed study (GA28948); those pooled results cannot be provided on the registry due to its limitations.

Comparison groups	Adalimumab v Etrolizumab
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2864 [21]
Method	Rank ANCOVA

Notes:

[21] - Nominal p-value; it has not been adjusted for multiplicity.

Secondary: Change From Baseline in MCS Stool Frequency Subscore at Week 6

End point title	Change From Baseline in MCS Stool Frequency Subscore at Week 6

End point description:

Stool frequency data were collected via the participant’s diaries and each day a participant provided a score from 0 to 3 according to the following definitions: 0 = normal number of stools; 1 = 1 to 2 more stools than normal; 2 = 3 to 4 more stools than normal; 3 = 5 or more stools than normal. The Mayo Clinic Score (MCS) stool frequency subscore was calculated as the average of three days daily diary scores closest to anchor dates at baseline and post-baseline. The data was considered non-parametric and was reported using RANK analysis of covariance (ANCOVA). Participants were stratified by concomitant treatment with corticosteroids or immunosuppressants at randomization and disease activity measured during screening (MCS ≤9/MCS ≥10); the model adjusted for these stratification factors along with the baseline stool frequency (SF) subscore.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	Placebo	Adalimumab	Etrolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	143	143	
Units: Score on a scale				
median (inter-quartile range (Q1-Q3))	0.0 (-1.0 to 0.0)	-1.0 (-1.0 to 0.0)	-1.0 (-1.0 to 0.0)	

Statistical analyses

Statistical analysis title	Etro vs. Placebo: MCS Stool Frequency at Week 6

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details.

Comparison groups	Placebo v Etrolizumab
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1729 [22]
Method	Rank ANCOVA

Notes:

[22] - p-value has been adjusted for multiplicity.

Statistical analysis title	Etro vs. Ada.: MCS Stool Frequency at Week 6

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details. Individual study results are shown, however, this endpoint was formally tested using pooled study data from this study and an identically designed study (GA28948); those pooled results cannot be provided on the registry due to its limitations.

Comparison groups	Adalimumab v Etrolizumab
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4174 [23]
Method	Rank ANCOVA

Notes:

[23] - Nominal p-value; it has not been adjusted for multiplicity.

Secondary: Change From Baseline in Ulcerative Colitis (UC) Bowel Movement Signs and Symptoms at Week 10, as Assessed by UC Patient-Reported Outcome Signs and Symptoms (UC-PRO/SS)

End point title	Change From Baseline in Ulcerative Colitis (UC) Bowel Movement Signs and Symptoms at Week 10, as Assessed by UC Patient-Reported Outcome Signs and Symptoms (UC-PRO/SS)

End point description:

The UC-PRO/SS questionnaire was collected in the e-diary and completed by participants for at least 9 to 12 consecutive days prior to a study visit. The bowel movement domain score ranges from 0 to 27, with a higher score indicating a worse disease state. The most recent 7 daily scores available (not including the visit) were selected for the calculation of the visit score. For each item in the questionnaire, a score was calculated for a visit by taking the average of the selected daily scores. The

domain score for a visit was calculated as the sum of the averaged items for each question. A Mixed Model for Repeated Measures (MMRM) analysis of the data included the fixed categorical effects of treatment, visit, study stratification factors, and treatment-by-visit interaction, and the continuous covariates of the baseline UC-PRO/SS domain and baseline UC-PRO/SS domain-by-visit interaction. An unstructured covariance matrix was used to model the within-patient errors within the MMRM.

End point type	Secondary

End point timeframe:

Baseline, Week 10

End point values	Placebo	Adalimumab	Etrolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59[24]	111[25]	108[26]	
Units: Score on a scale				
least squares mean (standard error)	-4.7 (± 0.7)	-5.9 (± 0.5)	-5.8 (± 0.5)	

Notes:

[24] - Only subjects with baseline and at least 1 post-baseline result were included.

[25] - Only subjects with baseline and at least 1 post-baseline result were included.

[26] - Only subjects with baseline and at least 1 post-baseline result were included.

Statistical analyses

Statistical analysis title	Etro vs. Placebo: UC Bowel Movement SS at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details. Individual study results are shown, however, this endpoint was formally tested using pooled study data from this study and an identically designed study (GA28948); those pooled results cannot be provided on the registry due to its limitations.

Comparison groups	Placebo v Etrolizumab
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1659 [27]
Method	Mixed Model for Repeated Measures
Parameter estimate	Mean difference (net)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	0.5

Notes:

[27] - Nominal p-value; it has not been adjusted for multiplicity.

Statistical analysis title	Etro vs. Ada.: UC Bowel Movement SS at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details. Individual study results are shown, however, this endpoint was formally tested using pooled study data from this study and an identically designed study (GA28948); those pooled results cannot be provided on the registry due to its limitations.

Comparison groups	Adalimumab v Etrolizumab

Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9182 [28]
Method	Mixed Model for Repeated Measures
Parameter estimate	Mean difference (net)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	1.4

Notes:

[28] - Nominal p-value; it has not been adjusted for multiplicity.

Secondary: Change From Baseline in UC Functional Symptoms at Week 10, as Assessed by UC-PRO/SS

End point title	Change From Baseline in UC Functional Symptoms at Week 10, as Assessed by UC-PRO/SS

End point description:

The UC-PRO/SS questionnaire was collected in the e-diary and completed by participants for at least 9 to 12 consecutive days prior to a study visit. The functional symptoms domain score ranges from 0 to 12, with a higher score indicating a worse disease state. The most recent 7 daily scores available (not including the visit) were selected for the calculation of the visit score. For each item in the questionnaire, a score was calculated for a visit by taking the average of the selected daily scores. The domain score for a visit was calculated as the sum of the averaged items for each question. A Mixed Model for Repeated Measures (MMRM) analysis of the data included the fixed categorical effects of treatment, visit, study stratification factors, and treatment-by-visit interaction, and the continuous covariates of the baseline UC-PRO/SS domain and baseline UC-PRO/SS domain-by-visit interaction. An unstructured covariance matrix was used to model the within-patient errors in the MMRM.

End point type	Secondary

End point timeframe:

Baseline, Week 10

End point values	Placebo	Adalimumab	Etrolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59[29]	111[30]	108[31]	
Units: Score on a scale				
least squares mean (standard error)	-1.0 (± 0.3)	-1.8 (± 0.2)	-2.0 (± 0.2)	

Notes:

[29] - Only subjects with baseline and at least 1 post-baseline result were included.

[30] - Only subjects with baseline and at least 1 post-baseline result were included.

[31] - Only subjects with baseline and at least 1 post-baseline result were included.

Statistical analyses

Statistical analysis title	Etro vs. Placebo: UC Functional SS at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details. Individual study results are shown, however, this endpoint was formally tested using pooled study data from this study and an identically designed study (GA28948); those pooled results

cannot be provided on the registry due to its limitations.

Comparison groups	Placebo v Etrolizumab
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0116 [32]
Method	Mixed Model for Repeated Measures
Parameter estimate	Mean difference (net)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	-0.2

Notes:

[32] - Nominal p-value; it has not been adjusted for multiplicity.

Statistical analysis title	Etro vs. Ada.: UC Functional SS at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details. Individual study results are shown, however, this endpoint was formally tested using pooled study data from this study and an identically designed study (GA28948); those pooled results cannot be provided on the registry due to its limitations.

Comparison groups	Adalimumab v Etrolizumab
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6771 [33]
Method	Mixed Model for Repeated Measures
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.5

Notes:

[33] - Nominal p-value; it has not been adjusted for multiplicity.

Secondary: Change From Baseline in Health-Related Quality of Life at Week 10, as Assessed by the Total Inflammatory Bowel Disease Questionnaire (IBDQ) Score

End point title	Change From Baseline in Health-Related Quality of Life at Week 10, as Assessed by the Total Inflammatory Bowel Disease Questionnaire (IBDQ) Score

End point description:

The IBDQ is a 32-item questionnaire containing four domains: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items). An overall total IBDQ score was computed by summing the individual 32-item scores. The range for the IBDQ total score is 32 to 224, with higher scores denoting better health-related quality of life. The unadjusted mean and standard deviation for each study arm are reported. The change from baseline in the IBDQ score was analyzed using an ANCOVA model taking the stratification factors used at randomization into account (concomitant treatment with corticosteroids or immunosuppressants at randomization and disease activity measured during screening [MCS ≤9/MCS ≥10]), and the baseline IBDQ score used as a

covariate.

End point type	Secondary

End point timeframe:

Baseline, Week 10

End point values	Placebo	Adalimumab	Etrolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62[34]	125[35]	125[36]	
Units: Score on a scale				
arithmetic mean (standard deviation)	31.2 (± 39.5)	34.8 (± 36.5)	36.2 (± 43.4)	

Notes:

[34] - Only subjects with baseline and at least 1 post-baseline result were included.

[35] - Only subjects with baseline and at least 1 post-baseline result were included.

[36] - Only subjects with baseline and at least 1 post-baseline result were included.

Statistical analyses

Statistical analysis title	Etro vs. Placebo: IBDQ Change at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details.

Comparison groups	Placebo v Etrolizumab
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4833 [37]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	15.2

Notes:

[37] - Nominal p-value; it has not been adjusted for multiplicity.

Statistical analysis title	Etro vs. Ada.: IBDQ Change at Week 10

Statistical analysis description:

Primary and secondary outcome measures were evaluated for statistical significance in a hierarchical manner with a component-wise multistage gatekeeping procedure. Please refer to the statistical analysis plan for details.

Comparison groups	Adalimumab v Etrolizumab

Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9931 [38]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	9.1

Notes:

[38] - Nominal p-value; it has not been adjusted for multiplicity.

Secondary: Pharmacokinetics of Etrolizumab: Serum Concentration

End point title	Pharmacokinetics of Etrolizumab: Serum Concentration[39]

End point description:

Serum concentrations of etrolizumab were evaluated at the primary endpoint visit (Week 10) and the secondary endpoint visit (Week 14). Both time points were two weeks after the most recent dose.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour) at Weeks 10 and 14

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK outcome measure of etrolizumab serum concentration was only assessed for those who had received etrolizumab.

End point values	Etrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	139			
Units: micrograms per millilitre (µg/mL)				
arithmetic mean (standard deviation)				
Week 10 (n = 137)	12.4 (± 5.51)			
Week 14 (n = 21)	15.5 (± 6.49)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With at Least One Adverse Event by Severity, According to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0)

End point title	Number of Participants With at Least One Adverse Event by Severity, According to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0)

End point description:

An adverse event (AE) is any untoward medical occurrence in a clinical investigation in which a patient is

administered a pharmaceutical product, regardless of causal attribution. The investigator independently assessed the severity and seriousness of each recorded AE. The AE severity grading scale for the NCI CTCAE v4.0 was used for assessing severity; any AE not specifically listed was rated according to the following grading scale from 1 to 5: 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, 5 = death. AEs of special interest (AESIs) included: elevated AST/ALT in combination with either elevated bilirubin or clinical jaundice; suspected transmission of infectious agent by the study drug; anaphylactic, anaphylactoid and systemic hypersensitivity reactions; and neurological signs, symptoms, and AEs that may suggest possible progressive multifocal leukoencephalopathy (PML).

End point type	Secondary

End point timeframe:

From Baseline until the end of study (up to 26 weeks)

End point values	Placebo	Adalimumab	Etrolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	143	143	
Units: Participants				
Any Adverse Event (AE)	33	62	63	
AE with Fatal Outcome	0	0	1	
Serious AE	5	3	7	
AE Leading to Study Treatment Discontinuation	1	2	4	
AE Leading to Dose Interruption	0	2	1	
Related AE	9	15	12	
AE by Worst Severity, Grade 1	14	29	30	
AE by Worst Severity, Grade 2	13	25	24	
AE by Worst Severity, Grade 3	6	8	8	
AE by Worst Severity, Grade 4	0	0	0	
AE by Worst Severity, Grade 5	0	0	1	
Any AESIs, Except for Hypersensitivity Reactions	0	0	0	
AESIs: Anaphylactic and Hypersensitivity Reactions	0	1	0	
Confirmed PML	0	0	0	
Infections	13	18	23	
Serious Infections	0	1	2	
Gastrointestinal Infections	1	0	3	
Opportunistic Infections	0	0	0	
Malignancies	0	2	0	
Injection Site Reactions	2	3	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants by Marked Laboratory Abnormality Status for Hematology Parameters as a Shift Table from Baseline to Week 10

End point title	Number of Participants by Marked Laboratory Abnormality Status for Hematology Parameters as a Shift Table from Baseline to Week 10

End point description:

Laboratory tests for hematology parameters were performed and values were compared with the Roche marked reference range. A marked abnormality was defined as a test result that was outside of the Roche marked reference range (labelled as 'High' or 'Low') and represented a clinically significant change from baseline. Not every laboratory abnormality qualified as an adverse event. A laboratory test result must have been reported as an adverse event if it met any of the following criteria: was accompanied by clinical symptoms; resulted in a change in study treatment or a medical intervention; or was clinically significant in the investigator's judgment. The results are presented as a shift from the baseline status to the post-baseline (Week 10) status. Baseline was defined as the last available assessment prior to first receipt of study drug. The 'missing' status included participants with missing baseline or post-baseline values. Abs = absolute count; Ery. = erythrocyte

End point type	Secondary

End point timeframe:

From Baseline up to Week 10

End point values	Placebo	Adalimumab	Etrolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	143	143	
Units: Participants				
Eosinophils Abs - Normal to Normal	63	133	124	
Eosinophils Abs - Normal to High	0	0	2	
Eosinophils Abs - Normal to Missing	7	9	15	
Eosinophils Abs - High to Normal	2	1	0	
Eosinophils Abs - High to High	0	0	1	
Eosinophils Abs - Missing to Normal	0	0	1	
Hematocrit - Low to Low	0	1	1	
Hematocrit - Low to Normal	3	2	5	
Hematocrit - Low to Missing	0	0	1	
Hematocrit - Normal to Low	0	1	2	
Hematocrit - Normal to Normal	62	128	119	
Hematocrit - Normal to Missing	7	10	14	
Hematocrit - Missing to Normal	0	1	1	
Hemoglobin - Low to Low	3	10	13	
Hemoglobin - Low to Normal	2	7	9	
Hemoglobin - Low to Missing	2	3	4	
Hemoglobin - Normal to Low	4	4	7	
Hemoglobin - Normal to Normal	56	113	99	
Hemoglobin - Normal to Missing	5	6	10	
Hemoglobin - Missing to Normal	0	0	1	
Lymphocytes Abs - Low to Low	2	2	2	
Lymphocytes Abs - Low to Normal	2	9	4	
Lymphocytes Abs - Low to Missing	0	0	1	
Lymphocytes Abs - Normal to Low	1	2	2	
Lymphocytes Abs - Normal to Normal	60	121	119	
Lymphocytes Abs - Normal to Missing	7	9	14	
Lymphocytes Abs - Missing to Normal	0	0	1	
Ery. Mean Corpuscular Volume - Normal to Low	0	1	1	
Ery. Mean Corpuscular Volume - Normal to Normal	65	130	126	
Ery. Mean Corpuscular Volume - Normal to Missing	7	9	15	

Ery. Mean Corpuscular Volume - High to High	0	1	0	
Ery. Mean Corpuscular Volume - High to Missing	0	1	0	
Ery. Mean Corpuscular Volume - Missing to Normal	0	1	1	
Neutrophils, Total, Abs - Low to Low	1	1	0	
Neutrophils, Total, Abs - Low to Normal	0	3	4	
Neutrophils, Total, Abs - Low to Missing	0	1	0	
Neutrophils, Total, Abs - Normal to Low	0	7	4	
Neutrophils, Total, Abs - Normal to Normal	55	105	105	
Neutrophils, Total, Abs - Normal to High	1	1	2	
Neutrophils, Total, Abs - Normal to Missing	8	7	15	
Neutrophils, Total, Abs - High to Normal	3	15	7	
Neutrophils, Total, Abs - High to High	4	1	5	
Neutrophils, Total, Abs - High to Missing	0	2	0	
Neutrophils, Total, Abs - Missing to Normal	0	0	1	
Platelets - Normal to Normal	59	128	116	
Platelets - Normal to High	1	0	3	
Platelets - Normal to Missing	9	9	15	
Platelets - High to Normal	2	2	4	
Platelets - High to High	1	2	2	
Platelets - High to Missing	0	1	2	
Platelets - Missing to Normal	0	1	1	
White Blood Cell Count - Low to Low	1	1	0	
White Blood Cell Count - Low to Normal	0	4	2	
White Blood Cell Count - Low to Missing	0	1	0	
White Blood Cell Count - Normal to Low	0	3	2	
White Blood Cell Count - Normal to Normal	64	123	124	
White Blood Cell Count - Normal to High	0	1	0	
White Blood Cell Count - Normal to Missing	7	8	14	
White Blood Cell Count - High to Normal	0	2	0	
White Blood Cell Count - Missing to Normal	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants by Marked Laboratory Abnormality Status for Chemistry Parameters as a Shift Table from Baseline to Week 10

End point title	Number of Participants by Marked Laboratory Abnormality Status for Chemistry Parameters as a Shift Table from Baseline to Week 10

End point description:

Laboratory tests for chemistry parameters were performed and values were compared with the Roche marked reference range. A marked abnormality was defined as a test result that was outside of the Roche marked reference range (labelled as 'High' or 'Low') and represented a clinically significant change from baseline. Not every laboratory abnormality qualified as an adverse event. A laboratory test

result must have been reported as an adverse event if it met any of the following criteria: was accompanied by clinical symptoms; resulted in a change in study treatment or a medical intervention; or was clinically significant in the investigator's judgment. The results are presented as a shift from the baseline status to the post-baseline (Week 10) status. Baseline was defined as the last available assessment prior to first receipt of study drug. The 'missing' status included participants with missing baseline or post-baseline values.

End point type	Secondary

End point timeframe:

From Baseline up to Week 10

End point values	Placebo	Adalimumab	Etrolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	143	143	
Units: Participants				
Albumin - Low to Normal	2	3	2	
Albumin - Low to Missing	0	0	2	
Albumin - Normal to Low	0	1	0	
Albumin - Normal to Normal	65	134	137	
Albumin - Normal to Missing	5	5	2	
Alkaline Phosphatase - Normal to Normal	67	138	137	
Alkaline Phosphatase - Normal to Missing	5	5	5	
Alkaline Phosphatase - High to Normal	0	0	1	
Alanine Aminotransferase - Normal to Normal	65	134	134	
Alanine Aminotransferase - Normal to High	0	1	0	
Alanine Aminotransferase - Normal to Missing	6	7	5	
Alanine Aminotransferase - High to Normal	1	1	2	
Alanine Aminotransferase - High to High	0	0	2	
Aspartate Aminotransferase - Normal to Normal	65	135	135	
Aspartate Aminotransferase - Normal to High	0	0	2	
Aspartate Aminotransferase - Normal to Missing	6	8	5	
Aspartate Aminotransferase - High to Normal	1	0	1	
Bicarbonate (CO2) - Low to Low	1	0	0	
Bicarbonate (CO2) - Low to Normal	1	3	0	
Bicarbonate (CO2) - Normal to Low	6	9	10	
Bicarbonate (CO2) - Normal to Normal	55	121	116	
Bicarbonate (CO2) - Normal to High	0	0	1	
Bicarbonate (CO2) - Normal to Missing	5	7	3	
Bicarbonate (CO2) - High to Normal	4	1	10	
Bicarbonate (CO2) - High to High	0	2	1	
Bicarbonate (CO2) - High to Missing	0	0	2	
Blood Urea Nitrogen - Normal to Normal	67	138	139	
Blood Urea Nitrogen - Normal to Missing	5	5	4	
Calcium - Normal to Normal	67	138	139	

Calcium - Normal to Missing	5	5	4	
Chloride - Low to Low	0	1	0	
Chloride - Low to Missing	0	1	0	
Chloride - Normal to Low	1	1	3	
Chloride - Normal to Normal	66	135	136	
Chloride - Normal to Missing	5	5	4	
Creatinine - Normal to Normal	67	138	139	
Creatinine - Normal to Missing	5	5	4	
Direct Bilirubin - Normal to Normal	66	132	137	
Direct Bilirubin - Normal to Missing	6	10	6	
Direct Bilirubin - Missing to Normal	0	1	0	
Potassium - Normal to Low	0	1	0	
Potassium - Normal to Normal	66	135	137	
Potassium - Normal to Missing	6	7	6	
Sodium - Normal to Normal	67	137	139	
Sodium - Normal to Missing	5	6	4	
Total Bilirubin - Normal to Normal	66	135	136	
Total Bilirubin - Normal to High	1	3	3	
Total Bilirubin - Normal to Missing	5	5	4	
Protein, Total - Low to Normal	1	0	1	
Protein, Total - Normal to Low	0	1	0	
Protein, Total - Normal to Normal	64	132	135	
Protein, Total - Normal to High	1	5	0	
Protein, Total - Normal to Missing	5	5	5	
Protein, Total - High to Normal	1	0	1	
Protein, Total - High to High	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Anti-Drug Antibodies (ADAs) to Etrolizumab at Baseline and Anytime Post-Baseline

End point title	Number of Participants With Anti-Drug Antibodies (ADAs) to Etrolizumab at Baseline and Anytime Post-Baseline[40]

End point description:

Anti-drug antibody (ADA) serum samples were collected from participants and analyzed using validated assays. Participants were considered to be ADA positive post-baseline if they were ADA negative or had missing data at baseline, but developed an ADA response following etrolizumab drug exposure (treatment-induced ADA response), or if they were ADA positive at baseline and the titer of one or more post-baseline samples was at least 0.60 titer units greater than the titer of the baseline sample (treatment-enhanced ADA response). Participants were considered to be ADA negative if they were ADA negative or had missing data at baseline and all post-baseline samples were negative, or if they were ADA positive at baseline but did not have any post-baseline samples with a titer that was at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

End point type	Secondary

End point timeframe:

Pre-dose (0 hour) on Day 1 and Week 4, Week 10, Week 14, and early termination/end of safety follow-up (up to 26 weeks)

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The immunogenicity outcome measure of ADAs to etrolizumab at baseline and post-baseline was only assessed for those who had received etrolizumab.

End point values	Etrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: Participants				
Positive for ADAs at Baseline (BL)	7			
Negative for ADAs at BL	134			
Post-BL: Positive for Treatment Emergent ADAs	26			
Post-BL ADA Positive: Treatment-Induced ADAs	26			
Post-BL ADA Positive: Treatment-Enhanced ADAs	0			
Post-BL: Negative for Treatment Emergent ADAs	115			
Post-BL ADA Negative: Treatment Unaffected	7			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline until the end of study (up to 26 weeks)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

The double-blinded treatment period consisted of a 10-week induction period and an additional 4-week treatment period for participants who met the definition of clinical remission at Week 10. Participants with moderate-to-severe ulcerative colitis who were naive to TNF inhibitors were randomized to this arm to receive placebo matching to etrolizumab subcutaneously (SC) once every 4 weeks (Q4W) up to Week 12 (at Weeks 0 [Day 1], 4, 8, and 12 [clinical remitters only]) and placebo matching to adalimumab SC once every 2 weeks (Q2W) up to Week 8 (at Weeks 0 [Day 1], 2, 4, 6, and 8).

Reporting group title	Adalimumab

Reporting group description:

The double-blinded treatment period consisted of a 10-week induction period and an additional 4-week treatment period for participants who met the definition of clinical remission at Week 10. Participants with moderate-to-severe ulcerative colitis who were naive to TNF inhibitors were randomized to this arm to receive adalimumab subcutaneously (SC) Q2W up to Week 8 (160 mg at Week 0 [Day 1], 80 mg at Week 2, 40 mg at Weeks 4, 6, and 8) and placebo matching to etrolizumab SC Q4W up to Week 12 (at Weeks 0 [Day 1], 4, 8, and 12 [clinical remitters only]).

Reporting group title	Etrolizumab

Reporting group description:

The double-blinded treatment period consisted of a 10-week induction period and an additional 4-week treatment period for participants who met the definition of clinical remission at Week 10. Participants with moderate-to-severe ulcerative colitis who were naive to TNF inhibitors were randomized to this arm to receive etrolizumab 105 mg subcutaneously (SC) Q4W up to Week 12 (at Weeks 0 [Day 1], 4, 8, and 12 [clinical remitters only]) and placebo matching to adalimumab SC Q2W up to Week 8 (at Weeks 0 [Day 1], 2, 4, 6, and 8).

Serious adverse events	Placebo	Adalimumab	Etrolizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 72 (6.94%)	3 / 143 (2.10%)	7 / 143 (4.90%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anaplastic oligodendroglioma			
subjects affected / exposed	0 / 72 (0.00%)	1 / 143 (0.70%)	0 / 143 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	2 / 72 (2.78%)	0 / 143 (0.00%)	0 / 143 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Sudden cardiac death			
subjects affected / exposed	0 / 72 (0.00%)	0 / 143 (0.00%)	1 / 143 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 72 (0.00%)	0 / 143 (0.00%)	1 / 143 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	2 / 72 (2.78%)	1 / 143 (0.70%)	1 / 143 (0.70%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon dysplasia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 143 (0.00%)	1 / 143 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 72 (1.39%)	0 / 143 (0.00%)	0 / 143 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 143 (0.00%)	1 / 143 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			

subjects affected / exposed	0 / 72 (0.00%)	0 / 143 (0.00%)	1 / 143 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 72 (1.39%)	0 / 143 (0.00%)	0 / 143 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Costochondritis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 143 (0.00%)	1 / 143 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 143 (0.00%)	1 / 143 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulpitis dental			
subjects affected / exposed	0 / 72 (0.00%)	0 / 143 (0.00%)	1 / 143 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 143 (0.70%)	0 / 143 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Adalimumab	Etrolizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 72 (19.44%)	23 / 143 (16.08%)	20 / 143 (13.99%)
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 72 (0.00%)	9 / 143 (6.29%)	3 / 143 (2.10%)
occurrences (all)	0	10	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 72 (6.94%)	2 / 143 (1.40%)	5 / 143 (3.50%)
occurrences (all)	5	2	5
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	8 / 72 (11.11%)	12 / 143 (8.39%)	11 / 143 (7.69%)
occurrences (all)	8	12	11
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 72 (5.56%)	3 / 143 (2.10%)	4 / 143 (2.80%)
occurrences (all)	5	4	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2014	Protocol Version 2: The protocol was amended to reflect recommendations following assessment of Protocol GA28949 through the Voluntary Harmonisation Procedure (VHP470) as follows: -The inclusion criteria was updated to include use of spermicide and barrier (rather than barrier alone) for acceptable methods of contraception during treatment period and for at least 24 weeks after the last dose. The inclusion criteria also identified combined oral contraceptive pills, and not progestin only pills, as acceptable and highly effective methods of contraception reflecting International Conference on Harmonisation (M3) guidance. -A new exclusion criterion was added to reflect that patients with suspicion of ischemic colitis, radiation colitis, or microscopic colitis will not be enrolled in the study. -The exclusion criterion regarding the history of moderate or severe allergic or anaphylactic/anaphylactoid reactions to chimeric, human, or humanized antibodies, fusion proteins, or murine proteins was updated to include hypersensitivity to etrolizumab (active drug substance) or any of the excipients (L-histidine, L-arginine, succinic acid, Polysorbate 20).
19 July 2014	Protocol Version 3: The protocol was amended to simplify the study design and to facilitate early access to open-label etrolizumab to eligible patients as follows: -Administration of adalimumab/adalimumab placebo at Weeks 10 and 12 was removed for all arms (for earlier washout) to facilitate earlier entry into the Open-Label Extension (OLE Part 1) of the OLE-SM (Open-Label Extension-Safety Monitoring) study (Study GA28951). Table "Study Drug Administration Schema" was updated accordingly. -Only patients achieving clinical remission at Week 10 will progress to Weeks 12 and 14 of the study to confirm maintenance of induction. Patients not achieving clinical remission at Week 10 should remain in the blinded study until Week 12 (to enable adalimumab washout) at which time they may enroll in the OLE.
18 September 2015	Protocol Version 4: The protocol was amended following FDA response to a type C request as follows: -Previously, the FDA had mandated a discontinuation of immunosuppressant therapy after Week 10 because of hypothetical risk of PML, resulting in distinct instructions regarding immunosuppressant use in different countries in the protocol. However, the Sponsor received agreement from the FDA to amend the global protocol GA28948 to instruct patients to continue their stable, baseline dose of immunosuppressants to the end of study treatment with dose reduction or discontinuation if patient experiences an immunosuppressant-related toxicity. Consequently the protocol was amended to allow patients to continue with immunosuppressant use from baseline to the end of study treatment (with dose reduction or discontinuation of immunosuppressant use permitted in the event of toxicity) in United States. -Following FDA feedback, inclusion criterion for patients at U.S. sites was amended to allow patients who had had an inadequate response to either immunosuppressants and/or corticosteroids to be eligible for the study rather than the previous requirement for failure to immunosuppressants with or without failure to corticosteroids. These two changes aligned United States with the rest of world regarding immunosuppressant use during the study and eligibility requirements for prior immunosuppressant/corticosteroid usage. Contents that indicated the use of immunosuppressants in the United States had to stop at Week 10 was removed.

18 December 2016	Protocol Version 5: The protocol was amended to update and align the safety section with information regarding potential risks for etrolizumab in the current Etrolizumab Investigator's Brochure, Version 10, and to account for a change in adalimumab formulation, as follows: -The protocol was amended to include the use of the new formulation of adalimumab as needed, when supplies of the current formulation (40 mg [0.8mL]) could no longer be procured. The new formulation consisted of 40 mg (0.4 mL) of adalimumab provided in a single-use, 1-mL, glass prefilled syringe with a fixed 29-gauge ½-inch needle. The efficacy, safety, and tolerability profile of the new formulation was comparable to that of the formulation currently in use (40 mg [0.8 mL]). -The protocol was updated and added to include potential hepatic effects to be in line with the safety profile of other anti-integrins, including vedolizumab, for which hepatic adverse events were reported. Although no clear hepatic safety signals emerged to date with etrolizumab, this potential risk was considered to be applicable across the anti-integrin class and would be evaluated in all etrolizumab studies.
30 August 2017	Protocol Version 6: The protocol was amended to enhance recruitment by reducing the complexity of the protocol, particularly at the time of screening and re-screening, as follows: -The requirement for obtaining Medical Monitor approval for extension of the screening period from 28 to 35 days was eliminated to accommodate logistic delays that might arise during the screening period and decrease site burden associated with placing approval requests. The screening window would not be extended beyond 35 days under any circumstances. -The time qualification for derivation of Mayo Clinic Score (MCS) baseline stool frequency and rectal bleeding subscores was redefined to include subscores obtained within 22 days prior to randomization (Day 1). Post-endoscopy subscores might be used, starting 2 days after the screening endoscopy, but only in cases where there were insufficient e-diary data to calculate these subscores prior to the bowel preparation day.
30 October 2018	Protocol Version 7: The protocol was amended primarily to reflect changes in efficacy endpoints. The changes would not impact study conduct at the site level. These changes are as follows: -To assess the onset of action of etrolizumab, secondary efficacy endpoints of change in Mayo Clinic Score (MCS) rectal bleeding and stool frequency subscores from baseline to Week 6 were added. -The secondary efficacy objective to evaluate colonic mucosal alphaE integrin concentration as a biomarker was expanded and would be evaluated as an exploratory efficacy endpoint to support additional biomarker candidate evaluations in the pivotal placebo-controlled studies within the etrolizumab Phase III Program. -Derivation of the MCS endoscopic subscore at post-baseline timepoints was amended to be consistent with emerging normative standards of endoscopic assessment in clinical trials (Sandborn et al. 2017). The sigmoid colon MCS endoscopic subscore would be used (rather than the score from the worst affected segment, i.e., rectum, sigmoid colon, or descending colon) if the baseline sigmoid colon MCS endoscopic subscore was 2-3. The sigmoid colon MCS endoscopic subscore was considered to be more reliable in assessing earlier treatment response.
15 March 2019	Protocol Version 8: The protocol was amended to provide further clarification and exploratory efficacy objectives was modified as follows: -Evaluation of response at Week 10, in subgroups by baseline expression levels of colonic tissue and/or peripheral blood biomarkers, was added to predict patient subgroups with a greater likelihood of responding to etrolizumab.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported