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

Summary

EudraCT number	2013-004280-31
Trial protocol	CZ DK DE HU SK PL
Global end of trial date	06 April 2020

Results information

Result version number	v1
This version publication date	15 April 2021
First version publication date	15 April 2021

Trial information

Trial identification

Sponsor protocol code	GA29102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02165215
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
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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	04 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of etrolizumab compared with placebo for remission of Ulcerative Colitis (UC) at Week 62 among patients with a clinical response at Week 10

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 August 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	Brazil: 43
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Czechia: 15
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	India: 53
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Mexico: 7
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Ukraine: 25
Country: Number of subjects enrolled	United States: 106
Country: Number of subjects enrolled	South Africa: 15
Worldwide total number of subjects	359
EEA total number of subjects	76

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)	343
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

359 patients entered the Induction phase of the study. For the double-blind maintenance phase, 102 patients were randomized and dosed to the Placebo arm and 108 to the Etrolizumab arm.

Period 1

Period 1 title	Induction Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open-Label Induction Phase: Etrolizumab

Arm description:

All participants will receive treatment with open-label etrolizumab 105 milligrams (mg) subcutaneous (SC) injection once every 4 weeks (Q4W) up to Week 10.

Arm type	Experimental
Investigational medicinal product name	Etrolizumab
Investigational medicinal product code	
Other name	RG7413, RO5490261, PRO145223, rhuMAb Beta7
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

105 mg once every 4 weeks (Q4W)

Number of subjects in period 1	Open-Label Induction Phase: Etrolizumab
Started	359
Dosed	358
Completed	336
Not completed	23
Consent withdrawn by subject	10
Physician decision	1
Non-Compliance	2
Adverse event, non-fatal	1
Lost to follow-up	6
Protocol deviation	1
Lack of efficacy	2

Period 2

Period 2 title	Maintenance Phase
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Maintenance Phase: Etrolizumab

Arm description:

Participants who achieved a clinical response at Week 10 during the induction phase and randomized to this arm for the double-blind maintenance phase will receive etrolizumab 105 mg SC injection Q4W from Week 12 up to Week 62.

Arm type	Experimental
Investigational medicinal product name	Etrolizumab
Investigational medicinal product code	
Other name	RG7413, RO5490261, PRO145223, rhuMAb Beta7
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

105 mg once every 4 weeks (Q4W)

Arm title	Double-Blind Maintenance Phase: Placebo

Arm description:

Participants who achieved a clinical response at Week 10 during the induction phase and randomized to this arm for the double-blind maintenance phase will receive placebo (matched to etrolizumab) SC injection Q4W from Week 12 up to Week 62.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matched to etrolizumab

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 was an induction phase of the study and all participants received the same treatment. The Maintenance phase (during which the test product was compared to placebo) has been reported as the baseline period to provide more relevant comparative data.

Number of subjects in period 2[2][3]	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo
Started	108	106
Dosed	108	102
Completed	96	101
Not completed	12	5
Consent withdrawn by subject	7	3

Adverse event, non-fatal	1	1
Lost to follow-up	2	-
Multiple reasons	2	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 210 participants were enrolled and dosed in the Maintenance phase. The worldwide number includes all participants in the Induction phase (n=359).

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Out of the participants that completed the Induction phase, only 210 met all criteria for dosing in the Maintenance phase.

Baseline characteristics

Reporting groups	
Reporting group title	Double-Blind Maintenance Phase: Etrolizumab
Reporting group description:	
Participants who achieved a clinical response at Week 10 during the induction phase and randomized to this arm for the double-blind maintenance phase will receive etrolizumab 105 mg SC injection Q4W from Week 12 up to Week 62.	
Reporting group title	Double-Blind Maintenance Phase: Placebo
Reporting group description:	
Participants who achieved a clinical response at Week 10 during the induction phase and randomized to this arm for the double-blind maintenance phase will receive placebo (matched to etrolizumab) SC injection Q4W from Week 12 up to Week 62.	

Reporting group values	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo	Total
Number of subjects	108	106	214
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)	104	104	208
From 65-84 years	4	2	6
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	38.3	39.2	
standard deviation	± 13.7	± 13.5	-
Sex: Female, Male			
Maintenance Phase			
Units:			
Female	48	54	102
Male	60	52	112
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2	2	4
Asian	21	13	34
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	6	8
White	79	78	157
More than one race	0	0	0
Unknown or Not Reported	4	7	11

End points

End points reporting groups

Reporting group title	Open-Label Induction Phase: Etrolizumab
Reporting group description:	
All participants will receive treatment with open-label etrolizumab 105 milligrams (mg) subcutaneous (SC) injection once every 4 weeks (Q4W) up to Week 10.	
Reporting group title	Double-Blind Maintenance Phase: Etrolizumab
Reporting group description:	
Participants who achieved a clinical response at Week 10 during the induction phase and randomized to this arm for the double-blind maintenance phase will receive etrolizumab 105 mg SC injection Q4W from Week 12 up to Week 62.	
Reporting group title	Double-Blind Maintenance Phase: Placebo
Reporting group description:	
Participants who achieved a clinical response at Week 10 during the induction phase and randomized to this arm for the double-blind maintenance phase will receive placebo (matched to etrolizumab) SC injection Q4W from Week 12 up to Week 62.	

Primary: Maintenance Phase: Percentage of Participants in Remission at Week 62 Among Randomized Participants with a Clinical Response at Week 10, as Determined by the Mayo Clinic Score (MCS)

End point title	Maintenance Phase: Percentage of Participants in Remission at Week 62 Among Randomized Participants with a Clinical Response at Week 10, as Determined by the Mayo Clinic Score (MCS)
End point description:	
MCS is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment. Clinical Response is MCS with ≥3-point decrease and 30% reduction from baseline as well as ≥1-point decrease in rectal bleeding subscore or an absolute rectal bleeding score of 0 or 1. Remission is MCS ≤2 with individual subscores ≤1 and a rectal bleeding subscore of 0.	
End point type	Primary
End point timeframe:	
Week 62	

End point values	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	102		
Units: percentage of participants				
number (not applicable)	29.6	20.6		

Statistical analyses

Statistical analysis title	Etrolizumab vs. Placebo
Comparison groups	Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1942
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted difference in response rates
Point estimate	7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	19.2

Secondary: Maintenance Phase: Percentage of Participants Who Maintained Clinical Remission at Week 62 Among Randomized Participants in Clinical Remission at Week 10, as Determined by the MCS

End point title	Maintenance Phase: Percentage of Participants Who Maintained Clinical Remission at Week 62 Among Randomized Participants in Clinical Remission at Week 10, as Determined by the MCS

End point description:

MCS is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment.

Clinical Remission is MCS ≤2 with individual subscores ≤1.

End point type	Secondary

End point timeframe:

Week 62

End point values	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	44		
Units: percentage of participants				
number (not applicable)	44.4	27.3		

Statistical analyses

Statistical analysis title	Etrolizumab vs. Placebo
Comparison groups	Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1524
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted difference in remission rates
Point estimate	14.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.55
upper limit	33.15

Secondary: Maintenance Phase: Percentage of Participants in Clinical Remission at Week 62, as Determined by the MCS

End point title	Maintenance Phase: Percentage of Participants in Clinical Remission at Week 62, as Determined by the MCS

End point description:

MCS is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment.

Clinical Remission is MCS ≤2 with individual subscores ≤1.

End point type	Secondary

End point timeframe:

Week 62

End point values	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	102		
Units: percentage of participants				
number (not applicable)	30.6	20.6		

Statistical analyses

Statistical analysis title	Etrolizumab vs. Placebo
Comparison groups	Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo

Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1466
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted difference in remission rates
Point estimate	8.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.26
upper limit	20.21

Secondary: Maintenance Phase: Percentage of Participants in Remission at Week 62 Among Randomized Participants in Remission at Week 10, as Determined by the MCS

End point title	Maintenance Phase: Percentage of Participants in Remission at Week 62 Among Randomized Participants in Remission at Week 10, as Determined by the MCS

End point description:

MCS is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment.

Remission is MCS ≤2 with individual subscores ≤1 and a rectal bleeding subscore of 0.

End point type	Secondary

End point timeframe:

Week 62

End point values	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	41		
Units: percentage of participants				
number (not applicable)	40.0	26.8		

Statistical analyses

Statistical analysis title	Etrolizumab vs. Placebo
Comparison groups	Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo

Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3083
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted difference in remission rates
Point estimate	10.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.72
upper limit	30.49

Secondary: Maintenance Phase: Percentage of Participants with Improvement from Baseline in Endoscopic Appearance of the Mucosa at Week 62, as Determined by the MCS Endoscopic Subscore

End point title	Maintenance Phase: Percentage of Participants with Improvement from Baseline in Endoscopic Appearance of the Mucosa at Week 62, as Determined by the MCS Endoscopic Subscore

End point description:

MCS is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment.

Improvement in endoscopic appearance of the mucosa is Endoscopy subscore ≤1.

End point type	Secondary

End point timeframe:

Baseline, Week 62

End point values	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	102		
Units: percentage of participants				
number (not applicable)	38.0	22.5		

Statistical analyses

Statistical analysis title	Etrolizumab vs. Placebo
Comparison groups	Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo

Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0235
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted difference in response rates
Point estimate	14.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.84
upper limit	26.28

Secondary: Maintenance Phase: Percentage of Participants with Endoscopic Remission at Week 62, as Determined by the MCS Endoscopic Subscore

End point title	Maintenance Phase: Percentage of Participants with Endoscopic Remission at Week 62, as Determined by the MCS Endoscopic Subscore

End point description:

MCS is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment.

Endoscopic Remission is Endoscopy subscore = 0.

End point type	Secondary

End point timeframe:

Week 62

End point values	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	102		
Units: percentage of participants				
number (not applicable)	30.6	16.7		

Statistical analyses

Statistical analysis title	Etrolizumab vs. Placebo
Comparison groups	Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo

Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0293
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted difference in remission rates
Point estimate	12.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.13
upper limit	23.89

Secondary: Maintenance Phase: Percentage of Participants with Histologic Remission at Week 62, as Determined by the Nancy Histological Index

End point title	Maintenance Phase: Percentage of Participants with Histologic Remission at Week 62, as Determined by the Nancy Histological Index

End point description:

Nancy Histological Index (NHI) is a 5-level classification ranging from grade 0 (No histologically significant disease) to grade 4 (severely active disease). Histologic remission is defined as a Nancy histological index of 0 or 1.

End point type	Secondary

End point timeframe:

Week 62

End point values	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	78		
Units: percentage of participants				
number (not applicable)	42.4	21.8		

Statistical analyses

Statistical analysis title	Etrolizumab vs. Placebo
Comparison groups	Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo

Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0075
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted difference in remission rates
Point estimate	19.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.16
upper limit	33.11

Secondary: Maintenance Phase: Percentage of Participants with Corticosteroid-Free Clinical Remission at Week 62 Among Participants Who Were Receiving Corticosteroids at Baseline, as Determined by the MCS

End point title	Maintenance Phase: Percentage of Participants with Corticosteroid-Free Clinical Remission at Week 62 Among Participants Who Were Receiving Corticosteroids at Baseline, as Determined by the MCS

End point description:

MCS is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment.

Clinical Remission is MCS ≤2 with individual subscores ≤1.

End point type	Secondary

End point timeframe:

Baseline, Week 62

End point values	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	50		
Units: percentage of participants				
number (not applicable)	18.2	8.0		

Statistical analyses

Statistical analysis title	Etrolizumab vs. Placebo
Comparison groups	Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1415
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted difference in remission rates
Point estimate	9.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.47
upper limit	23.13

Secondary: Maintenance Phase: Percentage of Participants with Corticosteroid-Free Remission at Week 62 Among Participants Who Were Receiving Corticosteroids at Baseline, as Determined by the MCS

End point title	Maintenance Phase: Percentage of Participants with Corticosteroid-Free Remission at Week 62 Among Participants Who Were Receiving Corticosteroids at Baseline, as Determined by the MCS

End point description:

MCS is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment.

Remission is MCS ≤2 with individual subscores ≤1 and a rectal bleeding subscore of 0.

End point type	Secondary

End point timeframe:

Baseline, Week 62

End point values	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	50		
Units: percentage of participants				
number (not applicable)	18.2	8.0		

Statistical analyses

Statistical analysis title	Etrolizumab vs. Placebo
Comparison groups	Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1415
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted difference in remission rates
Point estimate	9.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.47
upper limit	23.13

Secondary: Maintenance Phase: Change from Baseline to Week 62 in UC Bowel Movement Signs and Symptoms, as Assessed by the Ulcerative Colitis Patient-Reported Outcome Signs and Symptoms (UC-PRO/SS) Questionnaire

End point title	Maintenance Phase: Change from Baseline to Week 62 in UC Bowel Movement Signs and Symptoms, as Assessed by the Ulcerative Colitis Patient-Reported Outcome Signs and Symptoms (UC-PRO/SS) Questionnaire

End point description:

The UC-PRO questionnaire is collected in the e-diary and completed by participants for at least 9-12 consecutive days prior to a study visit. The UC-PRO is being reported in three domains; two domains are key endpoints and reported as UC-PRO Signs and Symptoms (UC-PRO/SS).

The bowel domain score ranges from 0-27, with a higher score indicating a worse disease state.

End point type	Secondary

End point timeframe:

Baseline, Week 62

End point values	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	73		
Units: score on a scale				
least squares mean (standard error)	-9.6 (± 0.8)	-6.7 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maintenance Phase: Change from Baseline to Week 62 in UC Functional Symptoms, as Assessed by the UC-PRO/SS Questionnaire

End point title	Maintenance Phase: Change from Baseline to Week 62 in UC Functional Symptoms, as Assessed by the UC-PRO/SS Questionnaire

End point description:

The UC-PRO questionnaire is collected in the e-diary and completed by participants for at least 9-12 consecutive days prior to a study visit. The UC-PRO is being reported in three domains; two domains are key endpoints and reported as UC-PRO Signs and Symptoms (UC-PRO/SS).

The functional domain score ranges from 0-12, with a higher score indicating a worse disease state.

End point type	Secondary

End point timeframe:

Baseline, Week 62

End point values	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	73		
Units: score on a scale				
least squares mean (standard error)	-3.0 (± 0.3)	-1.8 (± 0.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maintenance Phase: Change from Baseline to Week 62 in Health-Related Quality of Life, as Assessed by the Overall Score of the Inflammatory Bowel Disease Questionnaire (IBDQ)

End point title	Maintenance Phase: Change from Baseline to Week 62 in Health-Related Quality of Life, as Assessed by the Overall Score of the Inflammatory Bowel Disease Questionnaire (IBDQ)

End point description:

The IBDQ is used to assess participant's health-related quality of life (QOL). The 32-item questionnaire contains four domains: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items). The items are scored on a 7-point Likert scale with a higher score indicating better health-related QOL.

End point type	Secondary

End point timeframe:

Baseline, Week 62

End point values	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	102		
Units: Adjusted Mean				
number (not applicable)	66.9	64.8		

Statistical analyses

Statistical analysis title	Etro vs. Placebo
Comparison groups	Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6331
Method	ANCOVA
Parameter estimate	Difference in Adjusted Mean
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	10.8

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

End point description:

All adverse events (AEs) were graded for severity using the NCI-CTCAE v4.0. Any AE not specifically listed was assessed per the following 5 grades: Grade 1 = mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated. Grade 2 = moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living. Grade 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. Grade 4 = life-threatening consequences or urgent intervention indicated. Grade 5 = death related to AE. Not all grades are appropriate for all AEs; some AEs have fewer than 5 options. The terms "severe" and "serious" are not synonymous and are independently assessed for each AE. Multiple occurrences of AEs were counted only once per participant at the highest (worst) grade.

End point type	Secondary

End point timeframe:

From Baseline up to Week 74

End point values	Open-Label Induction Phase: Etrolizumab	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	358	108	102	
Units: participants				
Grade 1	95	24	23	
Grade 2	58	30	44	
Grade 3	24	14	15	
Grade 4	3	2	0	
Grade 5	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events Leading to Study Drug Discontinuation

End point title	Number of Participants with Adverse Events Leading to Study Drug Discontinuation

End point description:

End point type	Secondary

End point timeframe:

From Baseline up to Week 74

End point values	Open-Label Induction Phase: Etrolizumab	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	358	108	102	
Units: participants	9	5	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Serious Infection-Related Adverse Events

End point title	Number of Participants with Serious Infection-Related Adverse Events

End point description:

End point type	Secondary

End point timeframe:

From Baseline up to Week 74

End point values	Open-Label Induction Phase: Etrolizumab	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	358	108	102	
Units: participants	6	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Infection-Related Adverse Events by Severity, According to NCI-CTCAE v4.0

End point title	Number of Participants with Infection-Related Adverse Events by Severity, According to NCI-CTCAE v4.0

End point description:

All adverse events (AEs) were graded for severity using the NCI-CTCAE v4.0. Any AE not specifically listed was assessed per the following 5 grades: Grade 1 = mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated. Grade 2 = moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living. Grade 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. Grade 4 = life-threatening consequences or urgent intervention indicated. Grade 5 = death related to AE. Not all grades are appropriate for all AEs; some AEs have fewer than 5 options. The terms "severe" and "serious" are not synonymous and are independently assessed for each AE. Multiple occurrences of AEs were counted only once per participant at the highest (worst) grade.

End point type	Secondary

End point timeframe:

From Baseline up to Week 74

End point values	Open-Label Induction Phase: Etrolizumab	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	358	108	102	
Units: participants				
Grade 1	39	18	22	
Grade 2	21	17	10	
Grade 3	6	1	1	
Grade 4	0	1	0	
Grade 5	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Injection-Site Reactions by Severity, According to NCI-CTCAE v4.0

End point title	Number of Participants with Injection-Site Reactions by Severity, According to NCI-CTCAE v4.0

End point description:

All adverse events (AEs) were graded for severity using the NCI-CTCAE v4.0. Any AE not specifically listed was assessed per the following 5 grades: Grade 1 = mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated. Grade 2 = moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living. Grade 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. Grade 4 = life-threatening consequences or urgent intervention indicated. Grade 5 = death related to AE. Not all grades are appropriate for all AEs; some AEs have fewer than 5 options. The terms "severe" and "serious" are not synonymous and are independently assessed for each AE. Multiple occurrences of AEs were counted only once per participant at the highest (worst) grade.

End point type	Secondary

End point timeframe:

From Baseline up to Week 74

End point values	Open-Label Induction Phase: Etrolizumab	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	358	108	102	
Units: participants				
Grade 1	8	4	3	
Grade 2	0	0	0	
Grade 3	0	0	0	
Grade 4	0	0	0	
Grade 5	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Hypersensitivity Reaction Events by Severity, According to NCI-CTCAE v4.0

End point title	Number of Participants with Hypersensitivity Reaction Events by Severity, According to NCI-CTCAE v4.0

End point description:

All adverse events (AEs) were graded for severity using the NCI-CTCAE v4.0. Any AE not specifically listed was assessed per the following 5 grades: Grade 1 = mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated. Grade 2 = moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living. Grade 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. Grade 4 = life-threatening consequences or urgent intervention indicated. Grade 5 = death related to AE. Not all grades are appropriate for all AEs; some AEs have fewer than 5 options. The terms "severe" and "serious" are not synonymous and are independently assessed for each AE. Multiple occurrences of AEs were counted only once per participant at the highest (worst) grade.

End point type	Secondary

End point timeframe:

From Baseline up to Week 74

End point values	Open-Label Induction Phase: Etrolizumab	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	358	108	102	
Units: participants				
Grade 1	0	0	0	
Grade 2	1	0	0	
Grade 3	0	0	0	
Grade 4	0	0	0	
Grade 5	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Malignancies

End point title	Number of Participants with Malignancies

End point description:

End point type	Secondary

End point timeframe:

From Baseline up to Week 74

End point values	Open-Label Induction Phase: Etrolizumab	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	358	108	102	
Units: participants	0	2	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anti-Therapeutic Antibodies (ATAs) to Etrolizumab

End point title	Number of Participants with Anti-Therapeutic Antibodies (ATAs) to Etrolizumab

End point description:

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 12, 24, 44, and 62, and and Early Termination/End of Safety Follow-Up (up to Week 74)

End point values	Open-Label Induction Phase: Etrolizumab	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	337	108	102	
Units: participants	62	35	33	

Statistical analyses

No statistical analyses for this end point

Secondary: Maintenance Phase: Etrolizumab Serum Trough Concentration

End point title	Maintenance Phase: Etrolizumab Serum Trough Concentration

End point description:

Here 99999 represents data that were not analyzed as more than a third of the samples were below the lower limit of quantitation (LLOQ)

End point type	Secondary

End point timeframe:

Pre-dose (0 hour) at Baseline and Weeks 12, 24, 44, and 62

End point values	Double-Blind Maintenance Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	100		
Units: micrograms per millilitre (µg/mL)				
arithmetic mean (standard deviation)				
Week 12	7.66 (± 4.21)	7.63 (± 3.67)		
Week 24	10 (± 4.86)	99999 (± 99999)		
Week 44	10 (± 4.88)	99999 (± 99999)		
Week 62	15.4 (± 7.46)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to Week 74

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Open-Label Induction Phase: Etrolizumab

Reporting group description:

All participants will receive treatment with open-label etrolizumab 105 milligrams (mg) subcutaneous (SC) injection once every 4 weeks (Q4W) up to Week 10.

Reporting group title	Double-Blind Maintenance Phase: Placebo

Reporting group description:

Participants who achieved a clinical response at Week 10 during the induction phase and randomized to this arm for the double-blind maintenance phase will receive placebo (matched to etrolizumab) SC injection Q4W from Week 12 up to Week 62.

Reporting group title	Double-Blind Maintenance Phase: Etrolizumab

Reporting group description:

Participants who achieved a clinical response at Week 10 during the induction phase and randomized to this arm for the double-blind maintenance phase will receive etrolizumab 105 mg SC injection Q4W from Week 12 up to Week 62.

Serious adverse events	Open-Label Induction Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo	Double-Blind Maintenance Phase: Etrolizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 358 (4.75%)	8 / 102 (7.84%)	10 / 108 (9.26%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatine phosphokinase increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 358 (0.00%)	0 / 102 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 358 (0.00%)	0 / 102 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder cancer			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 358 (0.00%)	0 / 102 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 358 (0.00%)	1 / 102 (0.98%)	0 / 108 (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
Cardiac disorders			
Myocardial infarction			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 358 (0.28%)	0 / 102 (0.00%)	0 / 108 (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
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 358 (0.28%)	0 / 102 (0.00%)	0 / 108 (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
Bone marrow failure			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 358 (0.28%)	0 / 102 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 358 (0.00%)	0 / 102 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Systemic inflammatory response syndrome			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 358 (0.00%)	1 / 102 (0.98%)	0 / 108 (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
Gastrointestinal disorders			
Anal fistula			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 358 (0.28%)	0 / 102 (0.00%)	0 / 108 (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
Colitis ulcerative			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 358 (1.68%)	2 / 102 (1.96%)	2 / 108 (1.85%)
occurrences causally related to treatment / all	0 / 7	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 358 (0.28%)	0 / 102 (0.00%)	0 / 108 (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
Diarrhoea haemorrhagic			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 358 (0.00%)	1 / 102 (0.98%)	0 / 108 (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
Intestinal obstruction			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 358 (0.28%)	0 / 102 (0.00%)	0 / 108 (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
Intestinal perforation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 358 (0.28%)	0 / 102 (0.00%)	0 / 108 (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
Pancreatitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 358 (0.28%)	0 / 102 (0.00%)	0 / 108 (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
Hepatobiliary disorders			
Bile duct stone			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 358 (0.00%)	0 / 102 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 358 (0.00%)	2 / 102 (1.96%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 358 (0.28%)	0 / 102 (0.00%)	0 / 108 (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
Pneumonitis			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 358 (0.28%)	0 / 102 (0.00%)	0 / 108 (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
Pulmonary embolism			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 358 (0.00%)	1 / 102 (0.98%)	0 / 108 (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
Renal and urinary disorders			
Renal failure			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 358 (0.28%)	0 / 102 (0.00%)	0 / 108 (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			
Exostosis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 358 (0.00%)	0 / 102 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 358 (0.00%)	0 / 102 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 358 (0.00%)	0 / 102 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 358 (0.28%)	0 / 102 (0.00%)	0 / 108 (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
Hepatitis B			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 358 (0.28%)	0 / 102 (0.00%)	0 / 108 (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
Pulmonary tuberculosis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 358 (0.28%)	0 / 102 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 358 (0.28%)	1 / 102 (0.98%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 358 (0.28%)	0 / 102 (0.00%)	0 / 108 (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
Upper respiratory tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 358 (0.00%)	1 / 102 (0.98%)	0 / 108 (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
Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 358 (0.28%)	0 / 102 (0.00%)	0 / 108 (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

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

Non-serious adverse events	Open-Label Induction Phase: Etrolizumab	Double-Blind Maintenance Phase: Placebo	Double-Blind Maintenance Phase: Etrolizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 358 (17.88%)	54 / 102 (52.94%)	30 / 108 (27.78%)
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 358 (2.23%)	6 / 102 (5.88%)	0 / 108 (0.00%)
occurrences (all)	9	6	0
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 358 (0.28%)	9 / 102 (8.82%)	6 / 108 (5.56%)
occurrences (all)	1	11	9
Colitis ulcerative			
alternative assessment type: Systematic			
subjects affected / exposed	24 / 358 (6.70%)	34 / 102 (33.33%)	14 / 108 (12.96%)
occurrences (all)	24	35	16
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 358 (1.40%)	8 / 102 (7.84%)	4 / 108 (3.70%)
occurrences (all)	10	9	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	9 / 358 (2.51%)	11 / 102 (10.78%)	8 / 108 (7.41%)
occurrences (all)	11	11	10
Infections and infestations			

Nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	22 / 358 (6.15%)	3 / 102 (2.94%)	8 / 108 (7.41%)
occurrences (all)	22	4	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2014	The definition of moderate to severe UC was updated to include stool frequency sub-score of ≥1. Further, for MCS/pMCS calculation, the worst rectal bleeding score from the most recent 3 days prior to clinical visit was to be used; Endoscopy procedures for UC disease activity assessment were modified; further, in case of any discrepancy between local versus central endoscopy readers, an adjudication read was to be added; The dosage of etrolizumab to be administered was corrected from 100 mg to 105 mg. The dose of 100 mg was not administered to patients; PML assessment was modified to include the PML Subjective Checklist (symptom assessment) and the PML Objective Checklist (neurologic evaluation). The algorithm for evaluation of PML was updated; Exclusion criteria related to hepatitis C, CMV testing, patient's cancer history and stenosis and screening assessments related to JCV testing and the timing of endoscopy were revised; and The dosage and administration section was revised to include a 2-week window for delayed administration of study medication due to minor illness.
08 July 2014	The inclusion criterion regarding contraception use for women was amended to detail the use of spermicide and double barrier (rather than barrier alone) for acceptable methods of contraception during treatment period and for at least 24 weeks after the last dose (reflecting International Conference on Harmonisation (M3) guidance; A new exclusion criterion was added to exclude patients with suspicion of ischemic colitis, radiation colitis, or microscopic colitis; and 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).
22 August 2014	Local amendment only (US and Canada).
28 August 2015	The protocol was amended to remove the previous requirement that immunosuppressant use stop at Week 10 in the U.S. and Canada based on HA feedback. Instead, patients were allowed to continue with immunosuppressant use from baseline throughout induction and maintenance (with dose reduction or discontinuation of immunosuppressant use permitted in the event of toxicity) in the U.S. and Canada; and Inclusion criteria were modified to allow patients with inadequate response to either immunosuppressants or corticosteroids to be eligible for the study (rather than the previous requirement for failure to immunosuppressants with or without failure to corticosteroids).
24 August 2017	The protocol was amended to update and align the safety section with information regarding potential risks for etrolizumab in the etrolizumab Investigator's Brochure, Version 10, as follows. Guidelines for managing specific AEs were updated to include hepatic effects as a potential risk for etrolizumab, to be in line with the safety profile of other anti-integrins, including vedolizumab, for which hepatic AEs have been reported; Changes were also made to enhance recruitment by reducing the complexity of the protocol, particularly at the time of screening and re-screening, as follows: The minimum time between the diagnosis of ulcerative colitis (UC) and enrollment (Day 1) was reduced from 6 months to 3 months. This allowed patients with a more recent diagnosis of UC to be enrolled; The window for performing the endoscopy prior to Day 1 was extended from 10 to 16 days. The requirement for Medical Monitor approval for endoscopies conducted during this window was eliminated; and 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 Day 1.

27 August 2018	The protocol was primarily amended to reflect changes in efficacy endpoints. The changes would not impact study conduct at site level. The primary efficacy endpoint was changed to remission at Week 62 for patients who achieved clinical response (rather than remission) at Week 10, to align with clinical practice standards whereby patients who experienced a clinical response during treatment induction continued on treatment and were assessed for remission at a later time point; Secondary and exploratory efficacy endpoints were amended to align with the revision of the primary efficacy endpoint; To assess the onset of action of etrolizumab, a secondary efficacy endpoint of change in MCS rectal bleeding and stool frequency subscores from baseline to Week 6 was added; Histologic remission, defined as a Nancy histological index of ≤1, was added as a secondary efficacy outcome measure. The definition is based on consensus guidelines recommending that histologic remission should be defined by the absence of neutrophils in the crypts and lamina propria; 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; The sigmoid colon MCS endoscopic subscore will be used (rather than the score from the worst affected segment, i.e., rectum, sigmoid colon, or descending colon) if the baseline sigmoid colon MCS endoscopic subscore is 2-3. The sigmoid colon MCS endoscopic subscore is considered to be more reliable in assessing earlier treatment response; and Histologic activity on colon biopsies would be primarily measured using the Nancy histological index instead of the Geboes scale. Language regarding local injection-site reactions was clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported