Clinical trial results:
A Phase I, Open–Label, Randomized, Pharmacokinetic, Pharmacodynamic, And Safety Study Of Etrolizumab Followed By Open–Label Extension And Safety Monitoring In Pediatric Patients From 4 Years To Less Than 18 Years Of Age With Moderate To Severe Ulcerative Colitis Or Moderate To Severe Crohn's Disease

Summary

EudraCT number	2017-003649-10
Trial protocol	ES GB PL DE BE
Global end of trial date	

Results information

Result version number	v1
This version publication date	04 June 2020
First version publication date	04 June 2020

Trial information

Trial identification

Sponsor protocol code	CA40192

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03478956
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-001434-PIP01-13
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?	Yes

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	02 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 December 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetics and pharmacodynamics of etrolizumab in a pediatric inflammatory bowel disease patient population.

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 was conducted, whichever afforded the greater protection to the individual. The Informed Consent Forms and Child's Informed Assent Forms were signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 March 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	8
Adolescents (12-17 years)	16

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 30 patients were screened and 6 failed screenings, 2 due to administrative reasons and 4 due to failure to meet exclusion criteria; a total of 24 subjects were enrolled in the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Etrolizumab Q4W

Arm description:

Etrolizumab 1.5 milligrams per kilogram of body weight (mg/kg) was administered by subcutaneous (SC) injection once every 4 weeks (Q4W) for a total of 4 doses over the course of the 24-week randomized treatment phase (16-week treatment period plus 8-week safety follow-up). Participants were then given the option to participate in the 312-week open-label extension (OLE) treatment phase with etrolizumab 1.5 mg/kg SC Q4W followed by the 104-week safety surveillance phase (no etrolizumab treatment) to monitor for progressive multifocal leukoencephalopathy (PML). All participants who chose not to enter the OLE phase after the 24-week randomized treatment phase entered the 104-week PML monitoring phase.

Arm type	Experimental
Investigational medicinal product name	Etrolizumab
Investigational medicinal product code	RO5490261/F02-01
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

All participants randomized to this arm received 150 milligrams per millilitre (mg/mL) etrolizumab by subcutaneous injection of 0.01 mL per kilogram (kg) of body weight (1.5 mg/kg) once every 4 weeks (Q4W) during the 24-week randomized treatment phase. Following the completion of this phase, participants who chose to enter the open-label extension phase received 150 mg/mL etrolizumab by subcutaneous injection of 0.01 mL per kg of body weight (1.5 mg/kg) Q4W for up to 312 weeks.

Arm title	Etrolizumab Q8W

Arm description:

Etrolizumab 3.0 mg/kg was administered by subcutaneous (SC) injection once every 8 weeks (Q8W) for a total of 2 doses. Participants were then given the option to participate in the 312-week open-label extension (OLE) treatment phase with etrolizumab 1.5 mg/kg SC Q4W followed by the 104-week safety surveillance phase (no etrolizumab treatment) to monitor for progressive multifocal leukoencephalopathy (PML). All participants who chose not to enter the OLE phase after the 24-week randomized treatment phase entered the 104-week PML monitoring phase.

Arm type	Experimental
Investigational medicinal product name	Etrolizumab
Investigational medicinal product code	RO5490261/F02-01
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

All participants randomized to this arm received 150 milligrams per millilitre (mg/mL) etrolizumab by subcutaneous injection of 0.02 mL per kg of body weight (3 mg/kg) once every 8 weeks (Q8W) during

the 24-week randomized treatment phase. Following the completion of this phase, participants who chose to enter the open-label extension phase received 150 mg/mL etrolizumab by subcutaneous injection of 0.01 mL per kg of body weight (1.5 mg/kg) Q4W for up to 312 weeks.

Number of subjects in period 1	Etrolizumab Q4W	Etrolizumab Q8W
Started	12	12
Received at Least One Dose of Study Drug	12	12
Completed Randomized Treatment Phase	11	10
Started OLE Treatment Phase	11	10
Completed OLE Treatment Phase	0	0
Started PML Safety Monitoring Phase	1	2
Completed	0	0
Not completed	12	12
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	-
Ongoing in the Study	11	11

Baseline characteristics

Reporting groups	
Reporting group title	Etrolizumab Q4W
Reporting group description:	
Etrolizumab 1.5 milligrams per kilogram of body weight (mg/kg) was administered by subcutaneous (SC) injection once every 4 weeks (Q4W) for a total of 4 doses over the course of the 24-week randomized treatment phase (16-week treatment period plus 8-week safety follow-up). Participants were then given the option to participate in the 312-week open-label extension (OLE) treatment phase with etrolizumab 1.5 mg/kg SC Q4W followed by the 104-week safety surveillance phase (no etrolizumab treatment) to monitor for progressive multifocal leukoencephalopathy (PML). All participants who chose not to enter the OLE phase after the 24-week randomized treatment phase entered the 104-week PML monitoring phase.	
Reporting group title	Etrolizumab Q8W
Reporting group description:	
Etrolizumab 3.0 mg/kg was administered by subcutaneous (SC) injection once every 8 weeks (Q8W) for a total of 2 doses. Participants were then given the option to participate in the 312-week open-label extension (OLE) treatment phase with etrolizumab 1.5 mg/kg SC Q4W followed by the 104-week safety surveillance phase (no etrolizumab treatment) to monitor for progressive multifocal leukoencephalopathy (PML). All participants who chose not to enter the OLE phase after the 24-week randomized treatment phase entered the 104-week PML monitoring phase.	

Reporting group values	Etrolizumab Q4W	Etrolizumab Q8W	Total
Number of subjects	12	12	24
Age categorical Units: Subjects			
Children (2-11 years)	4	4	8
Adolescents (12-17 years)	8	8	16
Age Continuous Units: Years			
arithmetic mean	12.25	13.42	
standard deviation	± 3.62	± 4.46	-
Sex: Female, Male Units: Participants			
Male	8	5	13
Female	4	7	11
Race Units: Subjects			
White	12	12	24
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	12	11	23
Disease Indication: Crohn's Disease or Ulcerative Colitis Units: Subjects			
Crohn's Disease	5	5	10
Ulcerative Colitis	7	7	14
Randomization Stratification Factor: Body Weight <40 kg or ≥40 kg Units: Subjects			
<40 kg	5	4	9
≥40 kg	7	8	15

End points

End points reporting groups

Reporting group title	Etrolizumab Q4W

Reporting group description:

Etrolizumab 1.5 milligrams per kilogram of body weight (mg/kg) was administered by subcutaneous (SC) injection once every 4 weeks (Q4W) for a total of 4 doses over the course of the 24-week randomized treatment phase (16-week treatment period plus 8-week safety follow-up). Participants were then given the option to participate in the 312-week open-label extension (OLE) treatment phase with etrolizumab 1.5 mg/kg SC Q4W followed by the 104-week safety surveillance phase (no etrolizumab treatment) to monitor for progressive multifocal leukoencephalopathy (PML). All participants who chose not to enter the OLE phase after the 24-week randomized treatment phase entered the 104-week PML monitoring phase.

Reporting group title	Etrolizumab Q8W

Reporting group description:

Etrolizumab 3.0 mg/kg was administered by subcutaneous (SC) injection once every 8 weeks (Q8W) for a total of 2 doses. Participants were then given the option to participate in the 312-week open-label extension (OLE) treatment phase with etrolizumab 1.5 mg/kg SC Q4W followed by the 104-week safety surveillance phase (no etrolizumab treatment) to monitor for progressive multifocal leukoencephalopathy (PML). All participants who chose not to enter the OLE phase after the 24-week randomized treatment phase entered the 104-week PML monitoring phase.

Primary: Maximum Serum Concentration Observed (Cmax) of Etrolizumab

End point title	Maximum Serum Concentration Observed (Cmax) of Etrolizumab[1]

End point description:

Non-compartmental analysis methods were employed to calculate pharmacokinetics (PK) parameters. The PK Evaluable Population included all participants who received at least one dose of study drug and had evaluable PK data. This analysis included data from participants who had received their first dose (Day 1 for both arms) and last dose (on Day 56 for Q8W arm and Day 84 for Q4W arm) of study drug. The value '999999' indicates that the mean and standard deviation were not reported because 0 participants were assessed at that timepoint.

End point type	Primary

End point timeframe:

Postdose on Days 1, 56 (Q8W only), and 84 (Q4W only)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned for this study. All analyses were summarized by descriptive statistics.

End point values	Etrolizumab Q4W	Etrolizumab Q8W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: micrograms per millilitre (µg/mL)				
arithmetic mean (standard deviation)				
Day 1 (n = 10, 12)	7.73 (± 2.18)	19.0 (± 8.21)		
Day 56 (n = 0, 11)	999999 (± 999999)	18.1 (± 6.25)		
Day 84 (n = 11, 0)	9.80 (± 4.86)	999999 (± 999999)		

Statistical analyses

No statistical analyses for this end point

Primary: Time to Maximum Serum Concentration Observed (Tmax) of Etrolizumab

End point title	Time to Maximum Serum Concentration Observed (Tmax) of Etrolizumab[2]

End point description:

Non-compartmental analysis methods were employed to calculate pharmacokinetics (PK) parameters. The PK Evaluable Population included all participants who received at least one dose of study drug and had evaluable PK data. This analysis included data from participants who had received their first dose (Day 1 for both arms) and last dose (on Day 56 for Q8W arm and Day 84 for Q4W arm) of study drug. The value '999999' indicates that the mean and standard deviation were not reported because 0 participants were assessed at that timepoint.

End point type	Primary

End point timeframe:

Postdose on Days 1, 56 (Q8W only), and 84 (Q4W only)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned for this study. All analyses were summarized by descriptive statistics.

End point values	Etrolizumab Q4W	Etrolizumab Q8W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: Day				
arithmetic mean (standard deviation)				
Day 1 (n = 10, 12)	4.65 (± 1.43)	4.00 (± 1.48)		
Day 56 (n = 0, 11)	999999 (± 999999)	4.94 (± 3.28)		
Day 84 (n = 11, 0)	5.04 (± 2.92)	999999 (± 999999)		

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration-Time Curve Within a Dosing Interval (AUC-tau) of Etrolizumab

End point title	Area Under the Concentration-Time Curve Within a Dosing Interval (AUC-tau) of Etrolizumab[3]

End point description:

Non-compartmental analysis methods were employed to calculate pharmacokinetics (PK) parameters. The PK Evaluable Population included all participants who received at least one dose of study drug and had evaluable PK data. This analysis included data from participants who had received their last dose of study drug (on Day 56 for Q8W arm and Day 84 for Q4W arm). The value '999999' indicates that the mean and standard deviation were not reported because 0 participants were assessed at that timepoint.

End point type	Primary

End point timeframe:

Days 56 to 112 (Q8W only) and Days 84 to 112 (Q4W only)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned for this study. All analyses were summarized by descriptive statistics.

End point values	Etrolizumab Q4W	Etrolizumab Q8W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: Day*µg/mL				
arithmetic mean (standard deviation)				
AUC84-112 (n = 11, 0)	167 (± 86.9)	999999 (± 999999)		
AUC56-112 (n = 0, 10)	999999 (± 999999)	521 (± 306)		

Statistical analyses

No statistical analyses for this end point

Primary: Elimination Half-Life (t1/2) of Etrolizumab

End point title	Elimination Half-Life (t1/2) of Etrolizumab[4]

End point description:

Non-compartmental analysis methods were employed to calculate pharmacokinetics (PK) parameters. The PK Evaluable Population included all participants who received at least one dose of study drug and had evaluable PK data. This analysis included data from participants who had received their last dose of study drug (on Day 56 for Q8W arm and Day 84 for Q4W arm). The value '999999' indicates that the mean and standard deviation were not reported because 0 participants were assessed at that timepoint.

End point type	Primary

End point timeframe:

Days 56 (Q8W only) and 84 (Q4W only)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned for this study. All analyses were summarized by descriptive statistics.

End point values	Etrolizumab Q4W	Etrolizumab Q8W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: Day				
arithmetic mean (standard deviation)				
Day 56 (n = 0, 10)	999999 (± 999999)	8.65 (± 3.74)		
Day 84 (n = 11, 0)	7.31 (± 1.76)	999999 (± 999999)		

Statistical analyses

No statistical analyses for this end point

Primary: Steady-State Serum Concentration at the End of a Dosing Interval (Ctrough) of Etrolizumab

End point title	Steady-State Serum Concentration at the End of a Dosing Interval (Ctrough) of Etrolizumab[5]

End point description:

The Pharmacokinetics (PK) Evaluable Population included all participants who received at least one dose of study drug and had evaluable PK data. This analysis included data from participants at the end of each dosing interval (on Days 28, 56, 84, and 112 for Q4W arm and Days 56 and 112 for Q8W arm). The value '999999' indicates that the mean and standard deviation were not reported because 0 participants were assessed at that timepoint.

End point type	Primary

End point timeframe:

Predose on Days 28, 56, and 84, and Day 112

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned for this study. All analyses were summarized by descriptive statistics.

End point values	Etrolizumab Q4W	Etrolizumab Q8W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: micrograms per millilitre (µg/mL)				
arithmetic mean (standard deviation)				
Day 28 (n = 11, 0)	1.87 (± 1.32)	999999 (± 999999)		
Day 56 (n = 11, 11)	3.22 (± 2.24)	1.82 (± 1.99)		
Day 84 (n = 11, 0)	3.00 (± 2.38)	999999 (± 999999)		
Day 112 (n = 11, 10)	2.79 (± 2.01)	3.70 (± 4.64)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Baseline Absolute Numbers of Beta7 Receptor-Expressing Gut Homing CD3, CD4, and CD8 T Cells and CD19 B Cells with Unoccupied Beta7 Receptors in Peripheral Blood, Assessed by Flow Cytometry

End point title	Percentage of Baseline Absolute Numbers of Beta7 Receptor-Expressing Gut Homing CD3, CD4, and CD8 T Cells and CD19 B Cells with Unoccupied Beta7 Receptors in Peripheral Blood, Assessed by Flow Cytometry[6]

End point description:

Target engagement of etrolizumab was assessed via measurement of Beta7 receptor occupancy on Beta7 receptor expressing gut homing lymphocyte subsets in peripheral blood, including CD3, CD4, and CD8 T cells and CD19 B cells, using qualified flow cytometry methods. A decrease to 0% of baseline (BL) in median absolute cell counts of Beta7 receptor-expressing T and B cell subsets with unoccupied Beta7 receptors following etrolizumab treatment indicated maximal receptor occupancy by etrolizumab. The Pharmacodynamics (PD) Evaluable Population included all participants who received at least one dose of study treatment and had evaluable PD data.

End point type	Primary

End point timeframe:

Predose at Baseline (Day 1) and on Days 4, 56, 84, 98, and 112 (Treatment Period), and Days 126, 140, and 168 (Follow-Up Period)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned for this study. All analyses were summarized by descriptive statistics.

End point values	Etrolizumab Q4W	Etrolizumab Q8W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Percentage of BL Unoccupied Beta7 Cells				
median (standard deviation)				
CD3 T Cells: Baseline (n = 11, 10)	100 (± 0.0)	100 (± 0.0)		
CD3 T Cells: Day 4 (n = 8, 10)	0.18 (± 0.2)	0.40 (± 0.4)		
CD3 T Cells: Day 56 (n = 9, 10)	1.92 (± 1.9)	13.74 (± 13.5)		
CD3 T Cells: Day 84 (n = 9, 9)	7.43 (± 6.0)	1.06 (± 1.1)		
CD3 T Cells: Day 98 (n = 10, 9)	0.36 (± 0.4)	1.06 (± 1.1)		
CD3 T Cells: Day 112 (n = 10, 9)	4.06 (± 2.6)	6.01 (± 5.6)		
CD3 T Cells: Day 126 (n = 9, 8)	12.00 (± 12.0)	27.24 (± 24.6)		
CD3 T Cells: Day 140 (n = 9, 9)	47.47 (± 21.9)	56.82 (± 22.2)		
CD3 T Cells: Day 168 (n = 10, 9)	71.64 (± 22.4)	51.79 (± 23.1)		
CD4 T Cells: Baseline (n = 11, 10)	100 (± 0.0)	100 (± 0.0)		
CD4 T Cells: Day 4 (n = 8, 10)	0.17 (± 0.2)	0.00 (± 0.0)		
CD4 T Cells: Day 56 (n = 9, 10)	3.33 (± 3.3)	16.56 (± 16.1)		
CD4 T Cells: Day 84 (n = 9, 9)	7.14 (± 7.1)	1.28 (± 1.0)		
CD4 T Cells: Day 98 (n = 10, 9)	0.24 (± 0.2)	1.28 (± 1.3)		
CD4 T Cells: Day 112 (n = 10, 9)	3.60 (± 3.1)	6.74 (± 6.4)		
CD4 T Cells: Day 126 (n = 9, 8)	13.33 (± 13.3)	37.03 (± 33.7)		
CD4 T Cells: Day 140 (n = 9, 9)	55.34 (± 23.9)	62.01 (± 20.3)		
CD4 T Cells: Day 168 (n = 10, 9)	74.49 (± 26.1)	50.00 (± 16.3)		
CD8 T Cells: Baseline (n = 11, 10)	100 (± 0.0)	100 (± 0.0)		
CD8 T Cells: Day 4 (n = 8, 10)	0.00 (± 0.0)	0.00 (± 0.0)		
CD8 T Cells: Day 56 (n = 9, 10)	1.56 (± 1.6)	8.41 (± 8.4)		
CD8 T Cells: Day 84 (n = 9, 9)	2.72 (± 2.7)	0.00 (± 0.0)		
CD8 T Cells: Day 98 (n = 10, 9)	1.10 (± 1.1)	2.33 (± 2.3)		
CD8 T Cells: Day 112 (n = 10, 9)	0.97 (± 1.0)	2.46 (± 2.5)		
CD8 T Cells: Day 126 (n = 9, 8)	20.00 (± 20.0)	14.51 (± 14.5)		
CD8 T Cells: Day 140 (n = 9, 9)	54.17 (± 18.8)	40.98 (± 24.7)		
CD8 T Cells: Day 168 (n = 10, 9)	63.34 (± 40.1)	55.56 (± 21.1)		
CD19 B Cells: Baseline (n = 11, 10)	100 (± 0.0)	100 (± 0.0)		
CD19 B Cells: Day 4 (n = 8, 10)	0.00 (± 0.0)	0.00 (± 0.0)		
CD19 B Cells: Day 56 (n = 9, 10)	3.57 (± 3.6)	19.14 (± 17.1)		
CD19 B Cells: Day 84 (n = 9, 9)	10.71 (± 10.7)	0.00 (± 0.0)		
CD19 B Cells: Day 98 (n = 10, 9)	0.00 (± 0.0)	0.00 (± 0.0)		
CD19 B Cells: Day 112 (n = 9, 9)	7.14 (± 7.1)	7.14 (± 7.1)		
CD19 B Cells: Day 126 (n = 9, 8)	42.86 (± 21.4)	33.93 (± 32.3)		
CD19 B Cells: Day 140 (n = 9, 9)	68.00 (± 30.5)	77.78 (± 32.6)		
CD19 B Cells: Day 168 (n = 10, 9)	73.21 (± 17.7)	40.00 (± 13.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Adverse Events by Highest Severity Grade, Assessed According to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE v4.0)

End point title	Incidence of Adverse Events by Highest Severity Grade, Assessed 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 until last study visit or 12 weeks after the last dose of study drug, whichever was longer; up to the end of the randomized treatment phase (up to 24 weeks)

End point values	Etrolizumab Q4W	Etrolizumab Q8W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Participants				
Any Adverse Event - Any Grade	9	10		
Any Adverse Event - Grade 1	2	2		
Any Adverse Event - Grade 2	4	5		
Any Adverse Event - Grade 3	3	3		
Any Adverse Event - Grade 4	0	0		
Any Adverse Event - Grade 5	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Serious Infection-Related Adverse Events by Highest

Severity Grade, Assessed According to NCI-CTCAE v4.0

End point title	Incidence of Serious Infection-Related Adverse Events by Highest Severity Grade, Assessed According to NCI-CTCAE v4.0

End point description:

Serious infection-related AEs were graded for severity per 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 until last study visit or 12 weeks after the last dose of study drug, whichever was longer; up to the end of the randomized treatment phase (up to 24 weeks)

End point values	Etrolizumab Q4W	Etrolizumab Q8W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Hypersensitivity Reactions by Highest Severity Grade, Assessed According to NCI-CTCAE v4.0

End point title	Incidence of Hypersensitivity Reactions by Highest Severity Grade, Assessed According to NCI-CTCAE v4.0

End point description:

Hypersensitivity reactions 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 until last study visit or 12 weeks after the last dose of study drug, whichever was longer; up to the end of the randomized treatment phase (up to 24 weeks)

End point values	Etrolizumab Q4W	Etrolizumab Q8W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Malignancies by Highest Severity Grade, Assessed According to NCI-CTCAE v4.0

End point title	Incidence of Malignancies by Highest Severity Grade, Assessed According to NCI-CTCAE v4.0

End point description:

Malignancies 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 until last study visit or 12 weeks after the last dose of study drug, whichever was longer; up to the end of the randomized treatment phase (up to 24 weeks)

End point values	Etrolizumab Q4W	Etrolizumab Q8W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Anti-Drug Antibodies (ADAs) to Etrolizumab at Baseline and Post-Baseline

End point title	Incidence of Anti-Drug Antibodies (ADAs) to Etrolizumab at Baseline and Post-Baseline

End point description:

Participants were considered to be etrolizumab anti-drug antibody (ADA) positive if they were ADA negative or had missing data at Baseline (BL) but developed an ADA response following study drug exposure (i.e., treatment-induced ADA positive), or if they were ADA positive at baseline and the titer of one or more postbaseline samples was at least 0.60 titer unit greater than the titer of the baseline

sample (i.e., treatment-enhanced ADA positive); these ADA positive responses are summarized together (induced + enhanced) in the 'treatment-emergent ADA positive' category. Participants were considered to be ADA negative if they were ADA negative or had missing data at Baseline (BL) and all postbaseline samples were negative (i.e., treatment-emergent ADA negative), or if they are ADA positive at baseline but did not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (i.e., treatment unaffected).

End point type	Secondary

End point timeframe:

Days 1, 28, 84, 112, and 168 (up to the end of the randomized treatment phase at Week 24)

End point values	Etrolizumab Q4W	Etrolizumab Q8W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Participants				
Baseline (BL): ADA Positive	1	0		
BL: ADA Negative	11	12		
Post-BL: Treatment-Emergent ADA Positive	4	2		
Post-BL: Treatment-Induced ADA Positive	4	2		
Post-BL: Treatment-Enhanced ADA Positive	0	0		
Post-BL: Treatment-Emergent ADA Negative	7	10		
Post-BL: Treatment Unaffected	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Confirmed Progressive Multifocal Leukoencephalopathy (PML) During the 104-Week Post-Treatment PML Monitoring Phase

End point title	Incidence of Confirmed Progressive Multifocal Leukoencephalopathy (PML) During the 104-Week Post-Treatment PML Monitoring Phase

End point description:

The 104-week safety surveillance PML-monitoring phase (no etrolizumab treatment) will consist of telephone calls approximately every 6 months with administration of the protocol's PML Subjective Checklist. If there are any signs or symptoms suggestive of PML identified on this subjective checklist during the telephone call, the participant will be asked to come into the clinic for a neurologic examination. The protocol's PML Algorithm will be followed for any suspected case of PML, and any confirmed case of PML will be reported as a serious adverse event.

End point type	Secondary

End point timeframe:

Approximately every 6 months from last dose of study drug until the end of the PML monitoring phase (up to 104 weeks)

End point values	Etrolizumab Q4W	Etrolizumab Q8W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: Participants				

Notes:

[7] - Results are not available yet because 0 participants have completed the PML monitoring phase.

[8] - Results are not available yet because 0 participants have completed the PML monitoring phase.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline until last study visit or 12 weeks after the last dose of study drug, whichever was longer; up to the end of the randomized treatment phase (up to 24 weeks)

Adverse event reporting additional description:

After informed consent but prior to initiation of study drug, only serious AEs caused by protocol-mandated intervention were reported. After initiation of study drug, all AEs were reported until the last study visit or 12 weeks after the last dose of study drug. After this period, only serious AEs related to prior study drug were reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Etrolizumab Q8W

Reporting group description:

Etrolizumab 3.0 mg/kg was administered by subcutaneous (SC) injection once every 8 weeks (Q8W) for a total of 2 doses. Participants were then given the option to participate in the 312-week open-label extension (OLE) treatment phase with etrolizumab 1.5 mg/kg SC Q4W followed by the 104-week safety surveillance phase (no etrolizumab treatment) to monitor for progressive multifocal leukoencephalopathy (PML). All participants who chose not to enter the OLE phase after the 24-week randomized treatment phase entered the 104-week PML monitoring phase.

Reporting group title	Etrolizumab Q4W

Reporting group description:

Etrolizumab 1.5 milligrams per kilogram of body weight (mg/kg) was administered by subcutaneous (SC) injection once every 4 weeks (Q4W) for a total of 4 doses over the course of the 24-week randomized treatment phase (16-week treatment period plus 8-week safety follow-up). Participants were then given the option to participate in the 312-week open-label extension (OLE) treatment phase with etrolizumab 1.5 mg/kg SC Q4W followed by the 104-week safety surveillance phase (no etrolizumab treatment) to monitor for progressive multifocal leukoencephalopathy (PML). All participants who chose not to enter the OLE phase after the 24-week randomized treatment phase entered the 104-week PML monitoring phase.

Serious adverse events	Etrolizumab Q8W	Etrolizumab Q4W	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)	2 / 12 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ulcerative			

subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Etrolizumab Q8W	Etrolizumab Q4W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 12 (75.00%)	8 / 12 (66.67%)	
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	4 / 12 (33.33%)	
occurrences (all)	0	7	
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Polymenorrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Catarrh			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Investigations			
Weight decreased			
subjects affected / exposed	2 / 12 (16.67%)	2 / 12 (16.67%)	
occurrences (all)	2	2	
Injury, poisoning and procedural complications			

Arthropod bite			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 12 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Syncope			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 12 (8.33%)	3 / 12 (25.00%)	
occurrences (all)	1	3	
Lymphopenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 12 (16.67%)	3 / 12 (25.00%)	
occurrences (all)	4	3	
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Aphthous ulcer			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Colitis ulcerative			
subjects affected / exposed	0 / 12 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	1	

Crohn's disease			
subjects affected / exposed	2 / 12 (16.67%)	2 / 12 (16.67%)	
occurrences (all)	2	2	
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)	2 / 12 (16.67%)	
occurrences (all)	2	2	
Dyspepsia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Haematochezia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Odynophagia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	2 / 12 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	2	
Rash			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Rash papular			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Renal and urinary disorders			

Leukocyturia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Folliculitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Respiratory tract infection viral			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Varicella			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

Iron deficiency subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0	
Vitamin B12 deficiency subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 August 2018	Protocol CA40192 Version 2 was amended to clarify the exclusion criteria and the Schedule of Assessments for the open-label extension (OLE) phase: -Exclusion criteria for patients with strictures (stenosis) of the colon have been revised to exclude patients with fixed symptomatic stenosis of the intestine; -Exclusion criteria for the use of other biologics (e.g., anti-TNF) has been clarified; -Exclusion criteria has been deleted for tube feeding, defined formula diets, or parenteral alimentation/nutrition. Based on investigator feedback, this is a standard of care for patients with Crohn's disease. Including these treatments as a exclusion criterion reduces the potential patient pool at the sites; -The option for the administration of etrolizumab outside the clinic site has been removed; -The option of patients enrolling in the adult OLE studies of GA28951 and GA29145 has been deleted. Protocols GA28951 and GA29145 do not specify that patients from this study are eligible for enrollment; -Instructions about patient withdrawal from the RBR after site closure have been modified to indicate that the investigator must inform the Sponsor of patient withdrawal by emailing the study number and patient number; -Language regarding pregnancies in partners of male patients has been modified to account for the fact that some sites may not allow follow-up on partner pregnancies; -Language has been added for consistency with Roche's current data retention policy and to accommodate more stringent local requirements (if applicable); -Appendix 1c, Schedule of Assessments, for the OLE phase has been revised to list out every 4-week, 12-week and dosing visit time point.
22 November 2019	Protocol CA40192 Version 3 was amended to increase the number of participants and to extend the duration of the open-label extension (OLE) phase: -The total number of participants enrolled in the study was increased from approximately 16 to approximately 24, in order to achieve the requirement of 4 children from 4 years to <12 years of age with evaluable pharmacokinetic profiles; -The duration of the OLE was extended from 2 years to 6 years (312 weeks) in order to ensure that participants currently in the OLE will have drug available until the start of the pediatric Phase III program; -The end of study and length of study have been updated to include the extended duration of the OLE phase; -The Schedule of Assessments for the OLE phase has been revised to include the extended duration.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported