Clinical trial results:
An Open-Label Extension and Safety Monitoring Study of Moderate to Severe Ulcerative Colitis Patients Previously Enrolled in Etrolizumab Phase II/III Studies

Summary

EudraCT number	2013-004435-72
Trial protocol	GB SE DE CZ DK LV LT AT PT EE NL NO ES GR BE HR IT SK HU BG FR
Global end of trial date	05 October 2023

Results information

Result version number	v1 (current)
This version publication date	16 October 2024
First version publication date	16 October 2024

Trial information

Trial identification

Sponsor protocol code	GA28951

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02118584
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4058
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 October 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 October 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The aim of the study is to evaluate the efficacy and safety of etrolizumab in participants with ulcerative colities (UC).

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 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 204
Country: Number of subjects enrolled	Poland: 163
Country: Number of subjects enrolled	Russian Federation: 119
Country: Number of subjects enrolled	Ukraine: 157
Country: Number of subjects enrolled	Brazil: 118
Country: Number of subjects enrolled	Czechia: 125
Country: Number of subjects enrolled	Hungary: 86
Country: Number of subjects enrolled	France: 79
Country: Number of subjects enrolled	Canada: 74
Country: Number of subjects enrolled	Korea, Republic of: 67
Country: Number of subjects enrolled	Germany: 60
Country: Number of subjects enrolled	United Kingdom: 59
Country: Number of subjects enrolled	Italy: 50
Country: Number of subjects enrolled	Belgium: 49
Country: Number of subjects enrolled	Australia: 43
Country: Number of subjects enrolled	India: 39
Country: Number of subjects enrolled	Serbia: 33
Country: Number of subjects enrolled	Slovakia: 31
Country: Number of subjects enrolled	Bulgaria: 29
Country: Number of subjects enrolled	Israel: 25
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	New Zealand: 22

Country: Number of subjects enrolled	Lithuania: 21
Country: Number of subjects enrolled	South Africa: 17
Country: Number of subjects enrolled	Netherlands: 18
Country: Number of subjects enrolled	Estonia: 15
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Switzerland: 15
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Türkiye: 8
Country: Number of subjects enrolled	Latvia: 8
Country: Number of subjects enrolled	Malaysia: 7
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Colombia: 4
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hong Kong: 1
Worldwide total number of subjects	1822
EEA total number of subjects	796

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)	1724
From 65 to 84 years	98
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in this study in 42 countries. All participants who were enrolled in this study previously took part in one of the following parent studies - Phase II: GA27927; Phase III: GA28948, GA28949, GA28950, GA29102, GA29103.

Pre-assignment

Screening details:

Study consists of 2 parts, Part 1: Open-label extension (OLE) period & Part 2: Progressive multifocal leukoencephalopathy (PML) safety monitoring (SM) period. A total of 1822 participants were enrolled in study, 1773 participants in Part 1 & 796 participants in Part 2. Of the 796, 49 participants were directly enrolled into Part 2: PML SM period.

Period 1

Period 1 title	Part 1: Open Label Extension Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1 (OLE): Etrolizumab Only

Arm description:

Participants received etrolizumab 105 milligrams (mg), subcutaneously (SC) every 4 weeks (Q4W) for maximum of 369.9 weeks, followed by a 12-week safety follow-up.

Arm type	Experimental
Investigational medicinal product name	Etrolizumab
Investigational medicinal product code	RO5490261
Other name	RG7413, PRO145223, rhuMAb Beta7
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Etrolizumab, 105 mg, administered SC, Q4W for maximum of 369.9 weeks.

Arm title	Part 1 (OLE) to Part 2 (PML SM)

Arm description:

Participants received etrolizumab 105 mg, SC, Q4W for maximum of 369.9 weeks, followed by a 12-week safety follow-up in the OLE period. After the OLE period, participants were given the option to enter Part 2 (PML SM). Participants who chose to enter the PML SM period were monitored for PML for a maximum of 92-weeks, during which no etrolizumab treatment was administered.

Arm type	Experimental
Investigational medicinal product name	Etrolizumab
Investigational medicinal product code	RO5490261
Other name	RG7413, PRO145223, rhuMAb Beta7
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Etrolizumab, 105 mg, administered SC, Q4W for maximum of 369.9 weeks in Part 1 (OLE) only. No treatment was administered in Part 2 (PML SM).

Arm title	Part 2 (PML SM) Only

Arm description:

Participants from the Phase II or Phase III studies who were not eligible/did not wish to enroll in Part 1 (OLE), and had completed the 12-week safety follow-up period in their parent study were enrolled directly in Part 2 (PML SM). Participants were monitored for PML for a maximum of 92-weeks, during

which no etrolizumab treatment was administered.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Part 1 (OLE): Etrolizumab Only	Part 1 (OLE) to Part 2 (PML SM)	Part 2 (PML SM) Only
Started	1026	747	49
Completed	9	747	49
Not completed	1017	0	0
Physician decision	128	-	-
Reason Not specified	135	-	-
Adverse Event	79	-	-
Death	9	-	-
Unknown	3	-	-
Non-compliance	12	-	-
Withdrawal by Subject	568	-	-
Study Terminated by Sponsor	29	-	-
Lost to follow-up	53	-	-
Protocol deviation	1	-	-

Period 2

Period 2 title	Part 2: PML Safety Monitoring Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1 (OLE) to Part 2 (PML-SM)

Arm description:

After the OLE period, participants were given the option to enter the Part 2 (PML SM). Participants who chose to enter the PML SM period were monitored for PML for a maximum of 92-weeks, during which no etrolizumab treatment was administered.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Part 2: PML-SM Only

Arm description:

Participants from the Phase II or Phase III studies who were not eligible/did not wish to enroll in Part 1 (OLE), and had completed the 12-week safety follow-up period in their parent study were enrolled

directly in Part 2 (PML SM). Participants were monitored for PML for a maximum of 92-weeks, during which no etrolizumab treatment was administered.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2[1]	Part 1 (OLE) to Part 2 (PML-SM)	Part 2: PML-SM Only
Started	747	49
Completed	317	43
Not completed	430	6
Physician decision	10	1
Reason Not specified	6	-
Adverse Event	5	-
Death	1	-
Non-compliance	-	1
Withdrawal by Subject	32	1
Study Terminated by Sponsor	354	-
Lost to follow-up	22	3

Notes:

[1] - 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: Participants were given the option to enter the PML SM period. Only 747 participants chose to join this period.

Baseline characteristics

Reporting groups	
Reporting group title	Part 1 (OLE): Etrolizumab Only
Reporting group description:	
Participants received etrolizumab 105 milligrams (mg), subcutaneously (SC) every 4 weeks (Q4W) for maximum of 369.9 weeks, followed by a 12-week safety follow-up.	
Reporting group title	Part 1 (OLE) to Part 2 (PML SM)
Reporting group description:	
Participants received etrolizumab 105 mg, SC, Q4W for maximum of 369.9 weeks, followed by a 12-week safety follow-up in the OLE period. After the OLE period, participants were given the option to enter Part 2 (PML SM). Participants who chose to enter the PML SM period were monitored for PML for a maximum of 92-weeks, during which no etrolizumab treatment was administered.	
Reporting group title	Part 2 (PML SM) Only
Reporting group description:	
Participants from the Phase II or Phase III studies who were not eligible/did not wish to enroll in Part 1 (OLE), and had completed the 12-week safety follow-up period in their parent study were enrolled directly in Part 2 (PML SM). Participants were monitored for PML for a maximum of 92-weeks, during which no etrolizumab treatment was administered.	

Reporting group values	Part 1 (OLE): Etrolizumab Only	Part 1 (OLE) to Part 2 (PML SM)	Part 2 (PML SM) Only
Number of subjects	1026	747	49
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	39.7	40.7	42.7
standard deviation	± 13.3	± 14.1	± 15.2
Sex: Female, Male Units: participants			
Female	417	333	23
Male	609	414	26
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	1	1	1
Asian	101	40	4
Black or African American	11	18	0
White	843	635	40
Other	36	32	2
Unknown	33	20	2
Multiple	1	1	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	59	93	0
Not Hispanic or Latino	915	632	47
Unknown or Not Reported	52	22	2

Reporting group values	Total		
Number of subjects	1822		

Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	- -		
Sex: Female, Male Units: participants			
Female	773		
Male	1049		
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	3		
Asian	145		
Black or African American	29		
White	1518		
Other	70		
Unknown	55		
Multiple	2		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	152		
Not Hispanic or Latino	1594		
Unknown or Not Reported	76		

End points

End points reporting groups

Reporting group title	Part 1 (OLE): Etrolizumab Only
Reporting group description:	
Participants received etrolizumab 105 milligrams (mg), subcutaneously (SC) every 4 weeks (Q4W) for maximum of 369.9 weeks, followed by a 12-week safety follow-up.	
Reporting group title	Part 1 (OLE) to Part 2 (PML SM)
Reporting group description:	
Participants received etrolizumab 105 mg, SC, Q4W for maximum of 369.9 weeks, followed by a 12-week safety follow-up in the OLE period. After the OLE period, participants were given the option to enter Part 2 (PML SM). Participants who chose to enter the PML SM period were monitored for PML for a maximum of 92-weeks, during which no etrolizumab treatment was administered.	
Reporting group title	Part 2 (PML SM) Only
Reporting group description:	
Participants from the Phase II or Phase III studies who were not eligible/did not wish to enroll in Part 1 (OLE), and had completed the 12-week safety follow-up period in their parent study were enrolled directly in Part 2 (PML SM). Participants were monitored for PML for a maximum of 92-weeks, during which no etrolizumab treatment was administered.	
Reporting group title	Part 1 (OLE) to Part 2 (PML-SM)
Reporting group description:	
After the OLE period, participants were given the option to enter the Part 2 (PML SM). Participants who chose to enter the PML SM period were monitored for PML for a maximum of 92-weeks, during which no etrolizumab treatment was administered.	
Reporting group title	Part 2: PML-SM Only
Reporting group description:	
Participants from the Phase II or Phase III studies who were not eligible/did not wish to enroll in Part 1 (OLE), and had completed the 12-week safety follow-up period in their parent study were enrolled directly in Part 2 (PML SM). Participants were monitored for PML for a maximum of 92-weeks, during which no etrolizumab treatment was administered.	
Subject analysis set title	Part 1 (OLE): Etrolizumab
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received etrolizumab 105 mg, SC, Q4W for maximum of 369.9 weeks, followed by a 12-week safety follow-up.	
Subject analysis set title	Part 2: PML-SM
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants from Part 1 (OLE) and from Phase II/III studies who were not eligible/did not wish to enroll in Part 1 (OLE) and had completed the 12-week safety follow-up period were enrolled in the Part 2 (PML SM). Participants were monitored for PML for a maximum of 92-weeks, during which no etrolizumab treatment was administered.	

Primary: Part 1: Percentage of Participants With Clinical Remission as Determined by the Partial Mayo Clinic Score (pMCS)

End point title	Part 1: Percentage of Participants With Clinical Remission as Determined by the Partial Mayo Clinic Score (pMCS)[1]
End point description:	
The pMCS is a composite of 3 assessments, each rated from 0 (none) to 3 (severe disease): stool frequency, rectal bleeding, and physician's global assessment. The total score for pMCS ranges from 0 (none) to 9 (severe disease). pMCS clinical remission was defined as pMCS ≤ 2, a rectal bleeding score of 0-1, physician's global assessment of 0-1, stool frequency subscore of 0-1. Percentages have been rounded off. OLE Population included all participants who received at least one dose of open label etrolizumab in Part 1 of the study. Number analyzed is the number of participants with data available for analysis. "n"= number of participants with data available for analysis at the specified timepoint.	
End point type	Primary

End point timeframe:

Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, 312 and 324 weeks

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 statistical analysis was planned for this endpoint.

End point values	Part 1 (OLE): Etrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	1772			
Units: percentage of participants				
number (not applicable)				
Baseline (n=1772)	32.0			
Week 4 (n=1365)	47.2			
Week 8 (n=1302)	52.2			
Week 12 (n=1292)	55.9			
Week 24 (n=935)	63.7			
Week 36 (n=879)	68.3			
Week 48 (n=856)	73.4			
Week 60 (n=810)	72.2			
Week 72 (n=768)	75.4			
Week 84 (n=733)	76.5			
Week 96 (n=718)	72.2			
Week 108 (n=665)	72.0			
Week 120 (n=593)	77.4			
Week 132 (n=535)	82.2			
Week 144 (n=501)	80.0			
Week 156 (n=461)	78.5			
Week 168 (n=410)	81.0			
Week 180 (n=378)	78.8			
Week 192 (n=355)	80.8			
Week 204 (n=318)	83.6			
Week 216 (n=289)	84.8			
Week 228 (n=262)	85.1			
Week 240 (n=230)	82.6			
Week 252 (n=207)	86.0			
Week 264 (n=164)	84.8			
Week 276 (n=150)	86.0			
Week 288 (n=136)	82.4			
Week 300 (n=90)	86.7			
Week 312 (n=62)	87.1			
Week 324 (n=30)	80.0			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Percentage of Participants With Remission as Determined by the

Mayo Clinic Score (MCS)

End point title	Part 1: Percentage of Participants With Remission as Determined by the Mayo Clinic Score (MCS)[2]

End point description:

The Mayo Clinic scoring system is a composite of 4 assessments for UC disease activity. The 4 component sub-scores are: 1) stool frequency, 2) rectal bleeding, 3) flexible sigmoidoscopy scores, and 4) physician's global assessment, each rated from 03, 0 representing no pathology to 3 for severe disease. The minimum Mayo Score is 0 (no pathology) and the maximum is 12 (severe disease). MCS remission was defined as MCS ≤ 2, a rectal bleeding score of 0, physician's global assessment of 0-1, stool frequency subscore of 0-1 and endoscopy score of 0-1. Percentage has been rounded off. OLE Population included all participants who received at least one dose of open label etrolizumab in Part 1 of the study. Number analyzed is the number of participants with data available for analysis.

End point type	Primary

End point timeframe:

At OLE Week 108

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 statistical analysis was planned for this endpoint.

End point values	Part 1 (OLE): Etrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	623			
Units: percentage of participants				
number (not applicable)	58.1			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Participants With Serious Adverse Events (SAEs)

End point title	Part 1: Number of Participants With Serious Adverse Events (SAEs)[3]

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigation, whether or not considered related to the medicinal (investigational) product. A SAE is any significant hazard, contraindication, side effect that is fatal or life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is medically significant or requires intervention to prevent one or other of the outcomes listed above. OLE Population included all participants who received at least one dose of open label etrolizumab in Part 1 of the study.

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow up in OLE (approximately 7 years)

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 statistical analysis was planned for this endpoint.

End point values	Part 1 (OLE): Etrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	1773			
Units: participants	373			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Participants With Adverse Events (AEs) and Severity of AEs Assessed Using National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 [NCI CTCAE v4.0]

End point title	Part 1: Number of Participants With Adverse Events (AEs) and Severity of AEs Assessed Using National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 [NCI CTCAE v4.0][4]

End point description:

AE is any untoward medical occurrence in participant administered a pharmaceutical product & regardless of causal relationship with this treatment. It can be any unfavorable & unintended sign (including abnormal laboratory finding), symptom/disease temporally associated with use of investigational product, whether/not considered related to it. AEs were graded per NCI CTCAE v4.0.Grade 1=Mild; asymptomatic/mild symptoms; clinical /diagnostic observations only; intervention not indicated; Grade 2=Moderate; minimal, local/non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL);Grade 3= Severe/medically significant, but not immediately life-threatening; hospitalization/prolongation of hospitalization indicated; disabling; limiting self-care ADL; Grade 4=Life-threatening consequences/urgent intervention indicated; Grade 5=Death related to AE. OLE population=all participants who received at least 1 dose of open label etrolizumab in Part 1.

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow up in OLE (approximately 7 years)

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 statistical analysis was planned for this endpoint.

End point values	Part 1 (OLE): Etrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	1773			
Units: participants				
AEs, Any Grade	1431			
Grade 1 AEs	315			
Grade 2 AEs	679			
Grade 3 AEs	405			
Grade 4 AEs	23			
Grade 5 AEs	9			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Percentage of Participants With Endoscopic Remission

End point title	Part 1: Percentage of Participants With Endoscopic Remission[5]

End point description:

The Mayo scoring system is a composite of 4 assessments for UC disease activity. The 4 component sub-scores are: 1) stool frequency, 2) rectal bleeding, 3) flexible sigmoidoscopy scores, and 4) physician's global assessment, each rated from 03, 0 representing no pathology to 3 for severe disease. The minimum Mayo Score is 0 (no pathology) and the maximum is 12 (severe disease). Endoscopic remission was defined as Mayo Endoscopic subscore = 0. Percentage has been rounded off. OLE Population included all participants who received at least one dose of open label etrolizumab in Part 1 of the study. Number analyzed is the number of participants with data available for analysis.

End point type	Primary

End point timeframe:

At OLE Week 108

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 statistical analysis was planned for this endpoint.

End point values	Part 1 (OLE): Etrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	900			
Units: percentage of participants				
number (not applicable)	45.7			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Participants With Infection Related AEs and Severity of Infection-Related AEs Assessed Using NCI CTCAE v4.0

End point title	Part 1: Number of Participants With Infection Related AEs and Severity of Infection-Related AEs Assessed Using NCI CTCAE v4.0[6]

End point description:

AE=untoward medical occurrence in participant administered a pharmaceutical product & regardless of causal relationship with this treatment. It can be any unfavorable & unintended sign (including abnormal laboratory finding), symptom/disease temporally associated with use of investigational product, whether/not considered related to it. AEs were graded per NCI CTCAE v4.0.Grade 1=Mild; asymptomatic/mild symptoms; clinical/diagnostic observations only; intervention not indicated; Grade 2=Moderate; minimal, local/non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL); Grade 3= Severe/medically significant, but not immediately life-threatening; hospitalization/prolongation of hospitalization indicated; disabling; limiting self-care ADL; Grade 4=Life-threatening consequences/urgent intervention indicated; Grade 5=Death related to AE. OLE population=all participants who received at least 1 dose of open label etrolizumab in Part 1.

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow up in OLE (approximately 7 years)

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 statistical analysis was planned for this endpoint.

End point values	Part 1 (OLE): Etrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	1773			
Units: participants				
Infection Related AEs, Any Grade	825			
Infection Related AEs, Grade 1	576			
Infection Related AEs, Grade 2	423			
Infection Related AEs, Grade 3	96			
Infection Related AEs, Grade 4	6			
Infection Related AEs, Grade 5	1			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Participants With Serious Infection Related AES

End point title	Part 1: Number of Participants With Serious Infection Related AES[7]

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. A SAE is any significant hazard, contraindication, side effect that is fatal or life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is medically significant or requires intervention to prevent one or other of the outcomes listed above. OLE Population included all participants who received at least one dose of open label etrolizumab in Part 1 of the study.

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow up in OLE (approximately 7 years)

Notes:

[7] - 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 statistical analysis was planned for this endpoint.

End point values	Part 1 (OLE): Etrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	1773			
Units: participants	110			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Participants With Injection Site Reactions and Severity of Injection Site Reactions Assessed Using NCI CTCAE v4.0

End point title	Part 1: Number of Participants With Injection Site Reactions and Severity of Injection Site Reactions Assessed Using NCI

	CTCAE v4.0[8]

End point description:

AE=untoward medical occurrence in participant administered a pharmaceutical product & regardless of causal relationship with this treatment. It can be any unfavorable & unintended sign (including abnormal laboratory finding), symptom/disease temporally associated with use of investigational product, whether/not considered related to it. Injection-site reaction=any local reaction occurring at site of injection following drug administration. Signs (e.g. erythema, induration/swelling) & symptoms (e.g. pain, pruritus). Injection site reactions were graded as per NCI CTCAE v4.0. Grade 1=Tenderness with/without associated symptoms (e.g., warmth, erythema, itching); Grade 2=Pain; lipodystrophy; edema; phlebitis; Grade 3=Ulceration/necrosis; severe tissue damage; operative intervention indicated; Grade 4=life-threatening consequences/urgent intervention indicated; Grade=5 death related to AE. OLE population= all participants who received at least one dose of open label etrolizumab in Part 1.

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow up in OLE (approximately 7 years)

Notes:

[8] - 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 statistical analysis was planned for this endpoint.

End point values	Part 1 (OLE): Etrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	1773			
Units: participants				
Injection Site Reactions, Any Grade	32			
Injection Site Reactions, Grade 1	28			
Injection Site Reactions, Grade 2	5			
Injection Site Reactions, Grade 3	0			
Injection Site Reactions, Grade 4	0			
Injection Site Reactions, Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Participants With AEs Leading to Etrolizumab Discontinuation

End point title	Part 1: Number of Participants With AEs Leading to Etrolizumab Discontinuation[9]

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a Etrolizumab, whether or not considered related to the medicinal (investigational) product. Number of participants who discontinued etrolizumab treatment during the OLE period have been reported here. OLE Population included all participants who received at least one dose of open label etrolizumab in Part 1 of the study.

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow up in OLE (approximately 7 years)

Notes:

[9] - 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 statistical analysis was planned for this endpoint.

End point values	Part 1 (OLE): Etrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	1773			
Units: participants	234			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Participants with Malignancies

End point title	Part 1: Number of Participants with Malignancies[10]

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Number of participants who developed malignancies during the OLE period have been reported here. OLE Population included all participants who received at least one dose of open label etrolizumab in Part 1 of the study.

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow up in OLE (approximately 7 years)

Notes:

[10] - 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 statistical analysis was planned for this endpoint.

End point values	Part 1 (OLE): Etrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	1173			
Units: participants	38			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Participants with Hypersensitivity Reactions and Severity of Hypersensitivity Assessed Using NCI-CTCAE v4.0

End point title	Part 1: Number of Participants with Hypersensitivity Reactions and Severity of Hypersensitivity Assessed Using NCI-CTCAE v4.0[11]

End point description:

AE is any untoward medical occurrence in participant administered a pharmaceutical product & regardless of causal relationship with this treatment. It can be any unfavorable & unintended sign (including abnormal laboratory finding), symptom/disease temporally associated with use of investigational product, whether/not considered related to it. Hypersensitivity was assessed as per NCI CTCAE v4.0. 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. OLE Population included all participants who received at least one dose of open label etrolizumab in Part 1 of the study.

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow up in OLE (approximately 7 years)

Notes:

[11] - 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 statistical analysis was planned for this endpoint.

End point values	Part 1 (OLE): Etrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	1173			
Units: participants				
Hypersensitivity Reactions, Any Grade	85			
Hypersensitivity Reactions, Grade 1	65			
Hypersensitivity Reactions, Grade 2	19			
Hypersensitivity Reactions, Grade 3	4			

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Number of Participants with Confirmed Progressive Multifocal Leukoencephalopathy (PML) During the Post-Treatment PML Monitoring Period

End point title	Part 2: Number of Participants with Confirmed Progressive Multifocal Leukoencephalopathy (PML) During the Post-Treatment PML Monitoring Period[12]

End point description:

PML Safety Monitoring population included all participants who entered the PML SM period. No treatment was administered in PML SM period, and hence participants entering from Part 1 (OLE) and the parent studies have been reported together.

End point type	Primary

End point timeframe:

From end of safety follow-up in Part 1 or Phase II/III parent studies up to a maximum of 92 weeks

Notes:

[12] - 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 statistical analysis was planned for this endpoint.

End point values	Part 2: PML-SM			
Subject group type	Subject analysis set			
Number of subjects analysed	796			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part 1 (OLE): From Day 1 up to end of 12-week safety follow up in OLE (approximately 7 years); Part 2 (PML SM): From end of safety follow-up in Part 1 or Phase II/III parent studies up to a maximum of 92 weeks

Adverse event reporting additional description:

OLE population included all participants who received at least one dose of open label etrolizumab in Part 1 (OLE) of the study. PML SM population included all participants who entered the PML SM period. Part 2: PML SM arm includes all participants who entered PML SM from Part 1 (OLE) & from their respective parent studies.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Part 2 (PML SM)

Reporting group description:

Participants from Part 1 (OLE) and from Phase II/III studies who were not eligible/did not wish to enroll in Part 1 (OLE) and had completed the 12-week safety follow-up period were enrolled in the Part 2 (PML SM). Participants were monitored for PML for a maximum of 92-weeks, during which no etrolizumab treatment was administered.

Reporting group title	Part 1 (OLE): Etrolizumab

Reporting group description:

Participants received etrolizumab 105 mg, SC, Q4W for maximum of 369.9 weeks, followed by a 12-week safety follow-up.

Serious adverse events	Part 2 (PML SM)	Part 1 (OLE): Etrolizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 796 (0.25%)	373 / 1773 (21.04%)	
number of deaths (all causes)	1	9	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoma benign			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic renal cell carcinoma			

subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal papillary breast neoplasm			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin's disease			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour perforation			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal adenocarcinoma			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			

subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Breast cancer			
subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myeloid leukaemia			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Ovarian cancer			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenoma			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian stromal cancer			

subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of pharynx			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal neoplasm			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			

subjects affected / exposed	1 / 796 (0.13%)	0 / 1773 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-eclampsia			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chest pain			
subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Drug withdrawal syndrome			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperthermia			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Paraphimosis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abnormal uterine bleeding			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical dysplasia			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acquired hydrocele			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Benign prostatic hyperplasia			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical polyp			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hydrothorax			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Interstitial lung disease			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Post-traumatic stress disorder			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Cytomegalovirus test positive			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			

subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza A virus test positive			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiphyseal fracture			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine perforation			

subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprocedural myocardial infarction			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture displacement			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary contusion			

subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shoulder fracture			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropod bite			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			

subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniofacial fracture			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolysis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exposure to communicable disease			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Femur fracture			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epidural haemorrhage			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Heart disease congenital			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tethered oral tissue			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Cardiac failure congestive			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			
subjects affected / exposed	0 / 796 (0.00%)	4 / 1773 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paroxysmal atrioventricular block			

subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 796 (0.13%)	0 / 1773 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			

subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia vitamin B12 deficiency			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemoid reaction			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 796 (0.00%)	16 / 1773 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal polyp			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal dysplasia			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated umbilical hernia			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malocclusion			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
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 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids thrombosed			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon dysplasia			

subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic fistula			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			

subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 796 (0.00%)	5 / 1773 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune pancreatitis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 796 (0.00%)	6 / 1773 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			

subjects affected / exposed	1 / 796 (0.13%)	131 / 1773 (7.39%)	
occurrences causally related to treatment / all	0 / 1	4 / 153	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 796 (0.00%)	4 / 1773 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Biliary colic			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Granuloma skin			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioedema			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema nodosum			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Glomerulonephritis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvi-ureteric obstruction			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			

subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder perforation			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 796 (0.00%)	10 / 1773 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 796 (0.00%)	5 / 1773 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy			

subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seronegative arthritis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon laxity			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankylosing spondylitis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			

subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus infection			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 796 (0.13%)	13 / 1773 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial salpingitis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis listeria			

subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 796 (0.00%)	4 / 1773 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Endometritis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendiceal abscess			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 796 (0.00%)	11 / 1773 (0.62%)	
occurrences causally related to treatment / all	0 / 0	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			

subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Folliculitis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculous pleurisy			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			

subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 796 (0.00%)	10 / 1773 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 796 (0.00%)	6 / 1773 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Focal peritonitis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			

subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated tuberculosis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone abscess			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			

subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral infection			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus infection			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complicated appendicitis			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Latent tuberculosis			
subjects affected / exposed	0 / 796 (0.00%)	3 / 1773 (0.17%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			

subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 796 (0.00%)	2 / 1773 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 796 (0.00%)	7 / 1773 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	0 / 796 (0.00%)	1 / 1773 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part 2 (PML SM)	Part 1 (OLE): Etrolizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 796 (0.25%)	1052 / 1773 (59.33%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 796 (0.00%)	134 / 1773 (7.56%)	
occurrences (all)	0	187	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 796 (0.00%)	128 / 1773 (7.22%)	
occurrences (all)	0	149	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 796 (0.00%)	98 / 1773 (5.53%)	
occurrences (all)	0	117	
Colitis ulcerative			
subjects affected / exposed	2 / 796 (0.25%)	587 / 1773 (33.11%)	
occurrences (all)	2	882	
Diarrhoea			
subjects affected / exposed	0 / 796 (0.00%)	95 / 1773 (5.36%)	
occurrences (all)	0	114	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 796 (0.00%)	128 / 1773 (7.22%)	
occurrences (all)	0	172	
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 796 (0.00%)	165 / 1773 (9.31%)	
occurrences (all)	0	178	
Upper respiratory tract infection			
subjects affected / exposed	0 / 796 (0.00%)	110 / 1773 (6.20%)	
occurrences (all)	0	157	
Influenza			

subjects affected / exposed	0 / 796 (0.00%)	100 / 1773 (5.64%)	
occurrences (all)	0	121	
Nasopharyngitis			
subjects affected / exposed	0 / 796 (0.00%)	226 / 1773 (12.75%)	
occurrences (all)	0	344	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2014	1. The dose for each etrolizumab subcutaneous administration is changed from 100 mg to 105 mg. 2. Exclusion criterion has been amended to reflect that participants who developed cytomegalovirus (CMV) colitis were allowed to continue in the Phase III controlled studies following appropriate and successful treatment completion. 3. Exclusion criterion for participants that received fecal transplant during Phase III controlled studies has been removed. 4. Table 1 has been amended to reflect that in GA28950 controlled Phase III study any U.S. participants receiving immunosuppressants are to stop immunosuppressant use at Week 10. U.S. participants continuing on immunosuppressants after Week 10 are not permitted to enroll in the Part 1 (OLE) of this (GA28951) study. 5. In Table 1, footnote definitions of Clinical Relapse and Disease Worsening have been corrected. 6. It has been clarified that participants who were determined to be hepatitis B core antibody positive in the Phase III study should have hepatitis B DNA measured at defined timepoints in this (GA28951) study.
30 March 2014	1. The PML Assessment and Monitoring sections have been modified to include the PML Subjective Checklist (symptom assessment) and the PML Objective Checklist (neurologic evaluation) that are to be conducted according to the Schedule of Assessments. 2. Algorithm for the Evaluation of PML has been updated. 3. The UC disease activity sections have been updated to record stool frequency and rectal bleeding score for 5 days prior to clinic visit instead of recording daily. 4. Pharmacokinetic sample collection is added to schedule of assessment section.
04 July 2014	1. Risk mitigation strategy, including the potential risks associated with etrolizumab treatment and the risks associated with disease worsening has been updated in relevant sections. 2. The inclusion criterion regarding contraception use for women has been updated and a new appendix (Appendix 4) has been included. 3. Definition and reporting process of a Suspected Unexpected Serious Adverse Reaction (SUSAR) have been updated. 4. Footnote g in Appendix 1 (Schedule of Assessments) has been updated to clarify that results of the JCV antibody tests should be provided and discussed with the participants annually.

01 August 2014	1. The eligibility criteria for enrollment into Part 1 of OLE-SM GA28951 were amended to align with the design change in the Hibiscus studies. The achievement or non-achievement of clinical response criterion to enter OLE at Week 10 was updated to clinical remission. The language on the rescue medication was also updated according to the Hibiscus changes. 2. A new footnote for was added to include the definition of clinical remission. 3. Inclusion Criteria updated reducing the waiting time from 4 to 2 weeks for eligible participants to be transferred from Hibiscus to Part 1 of OLE-SM Study GA28951 after the Week 10 timepoint. 4. Inclusion Criteria updated to clarify when the first open-label etrolizumab dose can be administered to the participants who completed the Hibiscus studies at Week14. 5. Sections were updated to indicate new post-study adverse event reporting information. 7. "Unscheduled Visit" column, a "PML Objective Checklist" row, and extra footnotes added to Appendix 3 to clarify the assessments performed at the clinic in the event that the participants reports signs or symptoms of PML in between the scheduled site calls every 6 months.
13 January 2015	1. The eligibility criteria for enrollment amended to reflect that participants are to receive their first dose of etrolizumab in Study GA28951 4 weeks after their last dose of study medication in controlled Phase III Hibiscus studies, GA28948 and GA28949. 2. A new footnote added to include the definition of clinical remission. 3. Safety sub-sections updated. 5. A new section regarding protocol deviations was added. 6. A new "Unscheduled Visit" column, a "PML Objective Checklist" row was added to clarify the assessments performed at the clinic in the event that the participants reports signs or symptoms of PML in between the scheduled site calls every 6 months.
05 September 2017	1. Details about the number of participants exposed to etrolizumab was removed 2. Details on contraception methods was removed from the inclusion criteria. 3. Anti-therapeutic antibody samples must be collected at Week 0 if the Week 0 visit occurs > 7 days after the final visit of the Phase II OLE or Phase III controlled study.
12 February 2019	1. Language in the Background section was amended to align with the other ulcerative colitis studies in the Etrolizumab Phase III Program. 2. The duration of Part 1 OLE was updated to approximately 9 years. 3. Number of participants potentially enrolling in this study was updated to approximately 2100. 4. Janus kinase inhibitors added to the list of rescue therapies prohibited at any time during the study. 5. References to "Latvia/Lithuania" changed to "VHP" to reflect inclusion of all countries participating in the Voluntary Harmonisation Procedure. 6. Clarification regarding the reporting of adverse events related to medical device complaints in individuals other than the study participants added. 7. Procedures for adverse event reporting updated to clarify that sites are not expected to review participant-reported outcome data for adverse events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 October 2023	The study was terminated due to the Sponsor's decision to not pursue a marketing application for etrolizumab in adult UC indication.	-

Notes:

Limitations and caveats

None reported