Clinical trial results:
An Open-Label Extension and Safety Monitoring Study of Patients With Moderately to Severely Active Crohn's Disease Previously Enrolled in the Etrolizumab Phase III Protocol GA29144

Summary

EudraCT number	2014-003855-76
Trial protocol	SE EE LT LV HU DE ES NL SK CZ BE AT FR HR IT
Global end of trial date	09 October 2023

Results information

Result version number	v1
This version publication date	24 October 2024
First version publication date	24 October 2024

Trial information

Trial identification

Sponsor protocol code	GA29145

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02403323
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	09 October 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 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 Crohn's disease (CD).

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	08 June 2015
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	Russian Federation: 61
Country: Number of subjects enrolled	United States: 171
Country: Number of subjects enrolled	Poland: 51
Country: Number of subjects enrolled	Canada: 46
Country: Number of subjects enrolled	Czechia: 47
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Australia: 36
Country: Number of subjects enrolled	Brazil: 33
Country: Number of subjects enrolled	Hungary: 35
Country: Number of subjects enrolled	Ukraine: 27
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	Korea, Republic of: 23
Country: Number of subjects enrolled	New Zealand: 20
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	United Kingdom: 23
Country: Number of subjects enrolled	Israel: 15
Country: Number of subjects enrolled	Slovakia: 11
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Serbia: 10
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Switzerland: 9

Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Türkiye: 7
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	Latvia: 4
Country: Number of subjects enrolled	Lithuania: 6
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	South Africa: 4
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	Argentina: 1
Worldwide total number of subjects	790
EEA total number of subjects	300

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)	761
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in this study in 33 countries. All participants who enrolled into this study previously took part in study GA29144 (NCT02394028).

Pre-assignment

Screening details:

This study consists of 2 parts, Part 1: Open-label extension (OLE) period; Part 2: Progressive multifocal leukoencephalopathy (PML) safety monitoring (SM) period. 790 participants were enrolled in the study, 751 participants in Part 1 & 359 participants in Part 2. Of the 359, 39 participants directly entered Part 2 from study GA29144.

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), once every 4 weeks (Q4W) for a maximum of 320 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 320 weeks.

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

Arm description:

Participants received etrolizumab 105 mg, SC, Q4W for maximum of 320 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 320 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 study GA29144 who completed the 12-week safety follow-up period and were not eligible/did not wish to enroll in the Part 1 (OLE), enrolled directly in Part 2 (PML SM). Participant 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	431	320	39
Completed	5	320	39
Not completed	426	0	0
Physician decision	61	-	-
Adverse Event	26	-	-
Study Terminated By Sponsor	19	-	-
Death	3	-	-
Reason Not Specified	59	-	-
Unknown	1	-	-
Withdrawal by Subject	232	-	-
Non- compliance	2	-	-
Lost to follow-up	23	-	-

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 study GA29144 who completed the 12-week safety follow-up period and were not eligible/did not wish to enroll in the Part 1 (OLE), 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	320	39
Completed	112	33
Not completed	208	6
Physician decision	7	-
Adverse Event	4	-
Study Terminated By Sponsor	167	-
Death	1	-
Reason Not Specified	6	1
Unknown	1	-
Withdrawal by Subject	12	2
Non- compliance	1	-
Lost to follow-up	9	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 who discontinued Part1: OLE also had an option to enter the Part 2: PML SM phase. Hence, the number of participants who started Part 2: PML SM period is more than the participants who completed the Part1: OLE period.

Baseline characteristics

Reporting groups	
Reporting group title	Part 1 (OLE): Etrolizumab Only
Reporting group description:	
Participants received etrolizumab 105 milligrams (mg), subcutaneously (SC), once every 4 weeks (Q4W) for a maximum of 320 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 320 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 study GA29144 who completed the 12-week safety follow-up period and were not eligible/did not wish to enroll in the Part 1 (OLE), enrolled directly in Part 2 (PML SM). Participant 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	431	320	39
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	37.8	39.7	36.8
standard deviation	± 13.0	± 13.6	± 13.0
Sex: Female, Male Units: participants			
Female	199	158	19
Male	232	162	20
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	4	0
Asian	25	8	2
Black or African American	15	10	2
White	358	277	33
Multiple	2	1	0
Unknown	21	14	1
Other	10	6	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	24	24	3
Not Hispanic or Latino	385	280	35
Unknown or Not Reported	22	16	1

Reporting group values	Total		
Number of subjects	790		

Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	- -		
Sex: Female, Male Units: participants			
Female	376		
Male	414		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	4		
Asian	35		
Black or African American	27		
White	668		
Multiple	3		
Unknown	36		
Other	17		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	51		
Not Hispanic or Latino	700		
Unknown or Not Reported	39		

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), once every 4 weeks (Q4W) for a maximum of 320 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 320 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 study GA29144 who completed the 12-week safety follow-up period and were not eligible/did not wish to enroll in the Part 1 (OLE), enrolled directly in Part 2 (PML SM). Participant 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 study GA29144 who completed the 12-week safety follow-up period and were not eligible/did not wish to enroll in the Part 1 (OLE), 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 a maximum of 320 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 the study GA29144 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 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: Number of Participants with Crohn's Disease Activity Index (CDAI) Remission at 12-week Intervals

End point title	Part 1: Number of Participants with Crohn's Disease Activity Index (CDAI) Remission at 12-week Intervals[1]

End point description:

CDAI is a score obtained from composite of eight assessments: number of liquid or soft stools, abdominal pain, general well-being, presence of complications, taking lomotil (diphenoxylate/atropine) or other opiates for diarrhea, presence of an abdominal mass, hematocrit, and percentage deviation from standard weight. A decrease in CDAI over time indicates improvement in disease activity. CDAI scores range from 0 to 600. A higher score indicates worse outcome. A total score of less than 150 corresponds to remission. OLE population included all participants who received at least one dose of study drug in Study GA29145 Part 1 (OLE). "n"= number of participants with data available for analysis at the specified timepoint.

End point type	Primary

End point timeframe:

Day 1 and Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240 and 252 of OLE

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	751			
Units: participants				
Day 1 (n=751)	230			
Week 12 (n=354)	166			
Week 24 (n=285)	165			
Week 36 (n=250)	161			
Week 48 (n=163)	113			
Week 60 (n=198)	137			
Week 72 (n=180)	124			
Week 84 (n=160)	119			
Week 96 (n=119)	88			
Week 108 (n=123)	96			
Week 120 (n=109)	85			
Week 132 (n=97)	73			
Week 144 (n=87)	62			
Week 156 (n=80)	58			
Week 168 (n=81)	57			
Week 180 (n=73)	53			
Week 192 (n=50)	39			
Week 204 (n=46)	29			
Week 216 (n=44)	32			
Week 228 (n=33)	18			
Week 240 (n=24)	13			
Week 252 (n=21)	12			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Participants with Clinical Remission (CR) at 12-week Intervals

End point title	Part 1: Number of Participants with Clinical Remission (CR) at 12-week Intervals[2]

End point description:

Clinical remission was defined as a liquid/soft stool frequency (SF) mean daily score ≤3 and an abdominal pain (AP) mean daily score ≤1 with no worsening in either subscore compared to baseline, where the average was taken over 7 days prior to visit. Abdominal pain severity was assessed using the abdominal pain questionnaire which is an 11-point numeric rating scale with score ranging from 0 (no pain) to 10 (worse pain). Liquid/soft stool frequency was reported using the bristol stool form scale which classifies stools into seven groups based on its consistency. OLE population included all participants who received at least one dose of study drug in Study GA29145 Part 1 (OLE). "n"=number of participants with data available for analysis at the specified timepoint.

End point type	Primary

End point timeframe:

Day 1 and Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240 and 252 of OLE

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	751			
Units: participants				
Day 1 (n=751)	200			
Week 12 (n=397)	161			
Week 24 (n=346)	168			
Week 36 (n=302)	162			
Week 48 (n=244)	135			
Week 60 (n=231)	131			
Week 72 (n=221)	132			
Week 84 (n=193)	119			
Week 96 (n=171)	103			
Week 108 (n=141)	89			
Week 120 (n=128)	87			
Week 132 (n=116)	71			
Week 144 (n=106)	71			
Week 156 (n=102)	64			
Week 168 (n=97)	62			
Week 180 (n=88)	57			
Week 192 (n=67)	41			
Week 204 (n=53)	34			
Week 216 (n=53)	32			
Week 228 (n=45)	20			
Week 240 (n=29)	13			
Week 252 (n=23)	10			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Participants with Adverse Event (AE) and Severity of AEs as 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 Event (AE) and Severity of AEs as Assessed Using National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI-CTCAE v4.0)[3]

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. AEs were graded 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. Grade 4=Life threatening consequences, urgent intervention indicated; Grade 5=Death related to AE. OLE population included all participants who received at least one dose of study drug in study GA29145 Part 1 (OLE).

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow-up in OLE (approximately 6.3 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	751			
Units: participants				
AEs, Any Grade	624			
Grade 1 AEs	120			
Grade 2 AEs	259			
Grade 3 AEs	214			
Grade 4 AEs	27			
Grade 5 AEs	3			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Participants With Improvement in Simple Endoscopic Score for Crohn's Disease (SES-CD) Score at Week 108

End point title	Part 1: Number of Participants With Improvement in Simple Endoscopic Score for Crohn's Disease (SES-CD) Score at Week 108[4]

End point description:

SES-CD is an endoscopic score composite of 4 variables (ulcers size, percentage of ulcerated surface, inflamed surface, and presence of narrowing) in up to 5 ileocolonic segments (ileum right, colon, transverse colon, left colon, rectum) and scored on a scale of 0-3, with total score from 0-60. Higher score indicates higher ulcer surface/size in the 4 variables. Endoscopic improvement was defined as ≥50% reduction in SES-CD score compared to baseline. OLE population included all participants who received at least one dose of study drug in Study GA29145 Part 1 (OLE). Number analyzed is the number of participants with data available for analysis.

End point type	Primary

End point timeframe:

At OLE Week 108

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	242			
Units: participants	147			

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)[5]

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 popuation included all participants who received at least one dose of study drug in study GA29145 Part 1 (OLE).

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow up in OLE (approximately 6.3 years)

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	751			
Units: participants	206			

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.AE 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 as 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 one dose of study drug in GA29145 Part 1 (OLE).

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow up in OLE (approximately 6.3 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	751			
Units: participants				
Infection Related AEs, Any Grade	366			
Grade 1 Infection Related AEs	239			
Grade 2 Infection Related AEs	194			
Grade 3 Infection Related AEs	56			
Grade 4 Infection Related AEs	5			
Grade 5 Infection Related AEs	1			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Number of Participants with Adverse Events Leading to Etrolizumab Discontinuation

End point title	Part 1: Number of Participants with Adverse Events Leading to Etrolizumab Discontinuation[7]

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a 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 discontinued etrolizumab treatment during the OLE period have been reported here. OLE population included all participants who received at least one dose of study drug in study GA29145 Part 1 (OLE).

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow up in OLE (approximately 6.3 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	751			
Units: participants	112			

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[8]

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 study drug in study GA29145 Part 1 (OLE).

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow up in OLE (approximately 6.3 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	751			
Units: participants	58			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Incidence Rate of Infection-related Adverse Event

End point title	Part 1: Incidence Rate of Infection-related Adverse Event[9]

End point description:

AE=any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product & that does not necessarily have a causal relationship with this treatment. AE can therefore be any unfavorable & unintended sign (including abnormal laboratory finding), symptom/disease temporally associated with use of investigational product, whether/not considered related to the it. AE rate (per 100 participant years) = [Total number of AEs (in OLE only) / Total number of participant years at risk (in OLE only)]*100. Total participant-years at risk is the sum over all participants of the time intervals (in years) from first dose of study treatment in Part 1 (OLE) until participant completes/withdraws from study (including 12-week safety follow-up, if applicable). OLE

population=all participants who received at least one dose of study drug in study GA29145 Part 1 (OLE).

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow up in OLE (approximately 6.3 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	751			
Units: event per 100 participant-years				
number (confidence interval 95%)	62.74 (58.74 to 66.94)			

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[10]

End point description:

AE=untoward medical occurrence in participant administered a pharmaceutical product & regardless of causal relationship with this treatment.AE 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 the site of injection following study drug administration. Signs (e.g., erythema, induration/swelling) and symptoms (e.g., pain, pruritus). Injection site reactions were graded per NCI CTCAE v4.0.Grade 1=Tenderness with /without 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=participants who received at least 1 dose of study drug in study GA29145 Part

End point type	Primary

End point timeframe:

From Day 1 up to end of safety 12-week follow-up in OLE (approximately 6.3 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	751			
Units: participants				
Injection Site Reaction, Any Grade	15			
Injection Site Reaction, Grade 1	14			
Injection Site Reaction, Grade 2	1			
Injection Site Reaction, Grade 3	0			

Injection Site Reaction, Grade 4	0			
Injection Site Reaction, Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Number of Participants with Confirmed or Suspected Progressive Multifocal Leukoencephalopathy (PML)

End point title	Part 2: Number of Participants with Confirmed or Suspected Progressive Multifocal Leukoencephalopathy (PML)[11]

End point description:

PML was assessed by the PML Subjective Checklist (symptom assessment) and the PML Objective Checklist (neurologic evaluation). PML SM population included all participants who entered the PML SM phase. No treatment was administered in PML SM period, and hence participants entering from Part 1 (OLE) and the parent study have been reported together.

End point type	Primary

End point timeframe:

From end of safety follow-up in Part 1 or study GA29144 up to maximum of 92 weeks

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 2: PML SM			
Subject group type	Subject analysis set			
Number of subjects analysed	359			
Units: participants	0			

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[12]

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 study drug in study GA29145 Part 1 (OLE).

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow up in OLE (approximately 6.3 years)

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 1 (OLE): Etrolizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	751			
Units: participants	18			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Incidence Rate of Malignancies

End point title	Part 1: Incidence Rate of Malignancies[13]

End point description:

Malignancy rate (per 100 participant years) = [Total number of malignancies (in OLE only) / Total number of participant years at risk (in OLE only)]*100. Total participant-years at risk is the sum over all participants of the time intervals (in years) from the first dose of study treatment in Part 1 (OLE) until the participant completes/withdraws from the study (including the 12-week safety follow-up, if applicable). OLE population included all participants who received at least one dose of study drug in study GA29145 Part 1 (OLE).

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow up in OLE (approximately 6.3 years)

Notes:

[13] - 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	751			
Units: events per 100-participant-years				
number (confidence interval 95%)	1.85 (1.22 to 2.70)			

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[14]

End point description:

Hypersensitivity was reported using the MedDRA anaphylactic reaction standard MedDRA query (SMQ) & Sampson's criteria. 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 study drug in study GA29145 Part 1 (OLE).

End point type	Primary

End point timeframe:

From Day 1 up to end of 12-week safety follow up in OLE (approximately 6.3 years)

Notes:

[14] - 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	751			
Units: participants				
Hypersensitivity Reactions, Any Grade	3			
Hypersensitivity Reactions, Grade 1	2			
Hypersensitivity Reactions, Grade 2	0			
Hypersensitivity Reactions, Grade 3	1			

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 6.3 years); Part 2 (PML SM): From end of safety follow-up in Part 1 or in study GA29144 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 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 Part 2 (PML SM) from Part 1 (OLE) or from the parent study GA29144.

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 the study GA29144 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 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 a maximum of 320 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	1 / 359 (0.28%)	206 / 751 (27.43%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic malignant melanoma			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			

subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemangioma			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangioma			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Peripheral revascularisation			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal resection			

subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia repair			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implantable defibrillator insertion			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parenteral nutrition			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colectomy			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileostomy closure			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurosurgery			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion induced			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			

subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer haemorrhage			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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			
Varicocele			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Female genital tract fistula			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			

subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranasal sinus inflammation			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol abuse			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			

subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight increased			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy test negative			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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			

Postoperative ileus			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lisfranc fracture			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site haemorrhage			

subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Snake bite			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal anastomosis complication			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fall			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory impairment			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral artery stenosis			

subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 359 (0.00%)	6 / 751 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual field defect			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal perforation			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	10 / 751 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 359 (0.00%)	69 / 751 (9.19%)	
occurrences causally related to treatment / all	0 / 0	2 / 84	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal stenosis			

subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal stenosis			
subjects affected / exposed	0 / 359 (0.00%)	3 / 751 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 359 (0.00%)	5 / 751 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal prolapse			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal stenosis			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			

subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	3 / 751 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal stenosis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Noninfective gingivitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			

subjects affected / exposed	0 / 359 (0.00%)	5 / 751 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	10 / 751 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal fistula			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth disorder			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granulomatous liver disease			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Henoch-Schonlein purpura			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septal panniculitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panniculitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			

subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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			
Pain in extremity			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sacroiliitis			

subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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	0 / 359 (0.00%)	3 / 751 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Perineal abscess			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 359 (0.00%)	3 / 751 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	0 / 359 (0.00%)	3 / 751 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter infection			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella meningitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	0 / 359 (0.00%)	7 / 751 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Measles			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotavirus infection			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft infection			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 359 (0.28%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	13 / 751 (1.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal bacterial infection			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			

subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	0 / 359 (0.00%)	2 / 751 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 751 (0.13%)	
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 / 359 (0.56%)	453 / 751 (60.32%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 359 (0.00%)	76 / 751 (10.12%)	
occurrences (all)	0	96	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 359 (0.00%)	42 / 751 (5.59%)	
occurrences (all)	0	52	
Gastrointestinal disorders			

Crohn's disease			
subjects affected / exposed	1 / 359 (0.28%)	174 / 751 (23.17%)	
occurrences (all)	1	229	
Abdominal pain			
subjects affected / exposed	1 / 359 (0.28%)	82 / 751 (10.92%)	
occurrences (all)	2	109	
Vomiting			
subjects affected / exposed	0 / 359 (0.00%)	43 / 751 (5.73%)	
occurrences (all)	0	52	
Nausea			
subjects affected / exposed	0 / 359 (0.00%)	52 / 751 (6.92%)	
occurrences (all)	0	63	
Diarrhoea			
subjects affected / exposed	0 / 359 (0.00%)	53 / 751 (7.06%)	
occurrences (all)	0	68	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 359 (0.00%)	87 / 751 (11.58%)	
occurrences (all)	0	119	
Back pain			
subjects affected / exposed	0 / 359 (0.00%)	43 / 751 (5.73%)	
occurrences (all)	0	52	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 359 (0.00%)	80 / 751 (10.65%)	
occurrences (all)	0	136	
Upper respiratory tract infection			
subjects affected / exposed	0 / 359 (0.00%)	58 / 751 (7.72%)	
occurrences (all)	0	80	
Urinary tract infection			
subjects affected / exposed	1 / 359 (0.28%)	38 / 751 (5.06%)	
occurrences (all)	1	46	
COVID-19			
subjects affected / exposed	0 / 359 (0.00%)	80 / 751 (10.65%)	
occurrences (all)	0	81	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2014	The Abdominal Pain Questionnaire has been added to assess the severity of patient-reported abdominal pain.
04 November 2015	Addition of ileocolonoscopy and biopsy samples at Week 108
16 December 2016	1. Addition of potential hepatic effects 2. Eligibility criteria for Part 1 (OLE) changed. 3. First dose window increased.
14 May 2018	1. The definition of clinical relapse was clarified. 2. Patient-Reported Outcomes-2 (PRO2) was replaced with clinical remission (unweighted stool frequency and abdominal pain) to align with outcome measure changes in the parent study, GA29144. 3. The number of participants updated to align with the parent study, GA29144. 4. The exploratory outcome measure of simple endoscopic score for crohn's disease [SES-CD] score=0) at Week 108 replaced with the endoscopic outcome of SES-CD ≤4 (≤2 for ileal participants). 5. The definition of disease worsening updated to align with the parent study, GA29144. 6. The exclusion criteria updated to include participants who developed cytomegalovirus (CMV) colitis during Study GA29144 that led to early treatment discontinuation. 7. The directions for the biopsy pair collected at Week 108 was changed and was collected from the terminal ileum instead of the worst affected segment. 8. The requirement to assess and communicate baseline John Cunningham virus (JCV) antibody status to a participant was removed.
29 April 2019	1. The duration of Part 1 has been changed from 6.5 years to approximately 10 years. 2. Eligibility criteria have been changed to account for the closure of enrollment into the maintenance phase in parent study GA29144 after the projected sample size for this phase has been achieved. 3. Antagonists of IL-12 ±IL-23 (e.g., ustekinumab) have been added to the list of concomitant therapies prohibited. 4. Reference to participants with significant liver function test abnormalities has been removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

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

Notes:

Limitations and caveats

None reported