Clinical trial results:
A Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of CNTO 328 (Anti IL-6 Monoclonal Antibody) Plus Best Supportive Care Compared With Best Supportive Care in Subjects With Multicentric Castleman's Disease

Summary

EudraCT number	2009-012380-34
Trial protocol	GB BE ES DE FR NL HU
Global end of trial date	24 February 2017

Results information

Result version number	v1 (current)
This version publication date	11 March 2018
First version publication date	11 March 2018

Trial information

Trial identification

Sponsor protocol code	CNTO328MCD2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01024036
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202, Raritan, United States, NJ 08869
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.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	24 February 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of the study was to demonstrate that siltuximab in combination with best supportive care (BSC) was superior to BSC in terms of durable tumor and symptomatic response among subjects with Multicentric Castleman's Disease (MCD).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety was evaluated throughout the study and included adverse events (AEs), SAEs, routine clinical laboratory tests (hematology, chemistry, and coagulation), vital signs, ECGs, weight, infusion related reactions, and measurement for antibodies to study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	China: 16
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Egypt: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Russian Federation: 3

Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	79
EEA total number of subjects	15

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)	75
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

79 subjects were enrolled at 38 study centers in 19 countries. The first subject signed the informed consent on 09 Feb 2010, and the last subject's last visit for the primary analysis was 28 Feb 2013. The data until the end of study is presented here.

Pre-assignment

Screening details:

79 subjects were enrolled, randomized and treated during the blinded treatment period. 53 received siltuximab+best supportive care (BSC) and 26 received placebo+BSC.13 subjects who did not respond to placebo+BSC during the blinded treatment period, received siltuximab+BSC during the unblinded treatment period.

Period 1

Period 1 title	Blinded Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Siltuximab + Best Supportive Care (BSC)

Arm description:

Subjects received siltuximab 11 milligram per kilogram (mg/kg) as a 1-hour intravenous (IV) infusion every 3 weeks along with BSC until treatment failure, discontinuation of treatment, withdrawal from study, or until 48 weeks after last subject started study treatment, whichever occurred earlier. Subjects who discontinued treatment for any reason completed End-of-Treatment (EOT) Visit and entered Follow-up Period. If a subject had documented treatment failure and wished to continue treatment, subject’s treatment assignment was to be unblinded. Upon unblinding, if subejcts assigned to siltuximab, study treatment was to be discontinued, and the subject was to complete EOT Visit and enter Follow-up Period (up to 3 months after last study drug intake) wherein subjects were not received any study treatment and were followed until death, lost to follow up, withdrawal of consent, death of 50 percentage (%) of subjects, or end of the study, whichever occurred earlier.

Arm type	Experimental
Investigational medicinal product name	Siltuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received siltuximab 11 mg/kg as a 1-hour IV infusion every 3 weeks along with BSC until treatment failure, discontinuation of treatment, withdrawal from study, or until 48 weeks after last subject started study treatment, whichever occurred earlier.

Arm title	Placebo + Best Supportive Care (BSC)

Arm description:

Subjects received placebo as a 1-hour IV infusion every 3 weeks along with BSC until treatment failure, discontinuation of treatment, withdrawal from study, or until 48 weeks after last subject started study treatment, whichever occurred earlier. If a subject had documented treatment failure and wished to continue treatment, the subject’s treatment assignment was unblinded. Upon unblinding placebo subjects who received blinded treatment had an option to receive unblinded treatment with siltuximab. Subjects who discontinued or completed treatment period up to Week 48 and who consented to enter follow-up period were continued to be followed up during the course of follow-up period (up to 3 months after last study drug intake) wherein subjects were followed until death, lost to follow-up, withdrawal of consent, death of 50% of subjects, or end of the study, whichever occurred earlier.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received placebo as a 1-hour IV infusion every 3 weeks along with BSC until treatment failure, discontinuation of treatment, withdrawal from study, or until 48 weeks after last subject started study treatment, whichever occurred earlier.

Number of subjects in period 1	Siltuximab + Best Supportive Care (BSC)	Placebo + Best Supportive Care (BSC)
Started	53	26
Completed	31	6
Not completed	22	20
Adverse event, serious fatal	-	2
Physician decision	1	-
Consent withdrawn by subject	4	3
Adverse event, non-fatal	1	1
Lack of efficacy	16	14

Period 2

Period 2 title	Unblinded Treatment
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Placebo + Best Supportive Care (BSC)

Arm description:

Subjects received placebo as a 1-hour IV infusion every 3 weeks along with BSC until treatment failure, discontinuation of treatment, withdrawal from study, or until 48 weeks after last subject started study treatment, whichever occurred earlier. If a subject had documented treatment failure and wished to continue treatment, the subject’s treatment assignment was unblinded. Upon unblinding placebo subjects who received blinded treatment had an option to receive unblinded treatment with siltuximab. Subjects who discontinued or completed treatment period up to Week 48 and who consented to enter follow-up period were continued to be followed up during the course of follow-up period (up to 3 months after last study drug intake) wherein subjects were followed until death, lost to follow-up, withdrawal of consent, death of 50% of subjects, or end of the study, whichever occurred earlier.

Arm type	Experimental
Investigational medicinal product name	Siltuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects assigned to placebo crossover to siltuximab and received siltuximab 11 mg/kg as a 1-hour IV infusion every 3 weeks along with BSC.

Number of subjects in period 2[1]	Placebo + Best Supportive Care (BSC)
Started	13
Completed	10
Not completed	3
Adverse event, non-fatal	1
Lack of efficacy	2

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: Placebo subjects who had documented treatment failure and wished to continue treatment had an option to receive siltuximab during the unblinded treatment period.

Period 3

Period 3 title	Follow-up Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Siltuximab + Best Supportive Care (BSC)

Arm description:

Subjects received siltuximab 11 mg/kg as a 1-hour IV infusion every 3 weeks along with BSC until treatment failure, discontinuation of treatment, withdrawal from study, or until 48 weeks after last subject started study treatment, whichever occurred earlier. Subjects who discontinued treatment for any reason completed End-of-Treatment (EOT) Visit and entered Follow-up Period. If a subject had documented treatment failure and wished to continue treatment, subject's treatment assignment was to be unblinded. Upon unblinding, if subejcts assigned to siltuximab, study treatment was to be discontinued, and the subject was to complete EOT Visit and enter Follow-up Period (up to 3 months after last study drug intake) wherein subjects were not received any study treatment and were followed until death, lost to follow up, withdrawal of consent, death of 50% of subjects, or end of the study, whichever occurred earlier.

Arm type	Experimental
Investigational medicinal product name	Siltuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received siltuximab (11 mg/kg every 3 weeks) in the treatment period were followed up (up to 3 months after last study drug intake) until death, lost to follow up, withdrawal of consent, death of 50

percentage (%) of subjects, or end of the study, whichever occurred earlier.

Arm title	Placebo + Best Supportive Care (BSC)

Arm description:

Subjects received placebo as a 1-hour IV infusion every 3 weeks along with BSC until treatment failure, discontinuation of treatment, withdrawal from study, or until 48 weeks after last subject started study treatment, whichever occurred earlier. If a subject had documented treatment failure and wished to continue treatment, the subject's treatment assignment was unblinded. Upon unblinding placebo subjects who received blinded treatment had an option to receive unblinded treatment with siltuximab. Subjects who discontinued or completed treatment period up to Week 48 and who consented to enter follow-up period were continued to be followed up during the course of follow-up period (up to 3 months after last study drug intake) wherein subjects were followed until death, lost to follow-up, withdrawal of consent, death of 50% of subjects, or end of the study, whichever occurred earlier.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received matching placebo in the treatment period were continued to be followed up in follow-up period (up to 3 months after last study drug intake) until death, lost to follow up, withdrawal of consent, death of 50% of subjects, or the end of the study, whichever occurred earlier.

Number of subjects in period 3	Siltuximab + Best Supportive Care (BSC)	Placebo + Best Supportive Care (BSC)
Started	14	6
Completed	9	3
Not completed	5	3
Adverse event, serious fatal	4	1
Consent withdrawn by subject	-	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Siltuximab + Best Supportive Care (BSC)

Reporting group description:

Subjects received siltuximab 11 milligram per kilogram (mg/kg) as a 1-hour intravenous (IV) infusion every 3 weeks along with BSC until treatment failure, discontinuation of treatment, withdrawal from study, or until 48 weeks after last subject started study treatment, whichever occurred earlier. Subjects who discontinued treatment for any reason completed End-of-Treatment (EOT) Visit and entered Follow-up Period. If a subject had documented treatment failure and wished to continue treatment, subject's treatment assignment was to be unblinded. Upon unblinding, if subejcts assigned to siltuximab, study treatment was to be discontinued, and the subject was to complete EOT Visit and enter Follow-up Period (up to 3 months after last study drug intake) wherein subjects were not received any study treatment and were followed until death, lost to follow up, withdrawal of consent, death of 50 percentage (%) of subjects, or end of the study, whichever occurred earlier.

Reporting group title	Placebo + Best Supportive Care (BSC)

Reporting group description:

Subjects received placebo as a 1-hour IV infusion every 3 weeks along with BSC until treatment failure, discontinuation of treatment, withdrawal from study, or until 48 weeks after last subject started study treatment, whichever occurred earlier. If a subject had documented treatment failure and wished to continue treatment, the subject's treatment assignment was unblinded. Upon unblinding placebo subjects who received blinded treatment had an option to receive unblinded treatment with siltuximab. Subjects who discontinued or completed treatment period up to Week 48 and who consented to enter follow-up period were continued to be followed up during the course of follow-up period (up to 3 months after last study drug intake) wherein subjects were followed until death, lost to follow-up, withdrawal of consent, death of 50% of subjects, or end of the study, whichever occurred earlier.

Reporting group values	Siltuximab + Best Supportive Care (BSC)	Placebo + Best Supportive Care (BSC)	Total
Number of subjects	53	26	79
Title for AgeCategorical Units: subjects			
Adults (18-64 years)	51	24	75
From 65 to 84 years	2	2	4
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	44.4	47.7	
standard deviation	± 13.32	± 13.4	-
Title for Gender Units: subjects			
Female	23	4	27
Male	30	22	52

End points

End points reporting groups

Reporting group title	Siltuximab + Best Supportive Care (BSC)

Reporting group description:

Subjects received siltuximab 11 milligram per kilogram (mg/kg) as a 1-hour intravenous (IV) infusion every 3 weeks along with BSC until treatment failure, discontinuation of treatment, withdrawal from study, or until 48 weeks after last subject started study treatment, whichever occurred earlier. Subjects who discontinued treatment for any reason completed End-of-Treatment (EOT) Visit and entered Follow-up Period. If a subject had documented treatment failure and wished to continue treatment, subject's treatment assignment was to be unblinded. Upon unblinding, if subejcts assigned to siltuximab, study treatment was to be discontinued, and the subject was to complete EOT Visit and enter Follow-up Period (up to 3 months after last study drug intake) wherein subjects were not received any study treatment and were followed until death, lost to follow up, withdrawal of consent, death of 50 percentage (%) of subjects, or end of the study, whichever occurred earlier.

Reporting group title	Placebo + Best Supportive Care (BSC)

Reporting group description:

Subjects received placebo as a 1-hour IV infusion every 3 weeks along with BSC until treatment failure, discontinuation of treatment, withdrawal from study, or until 48 weeks after last subject started study treatment, whichever occurred earlier. If a subject had documented treatment failure and wished to continue treatment, the subject's treatment assignment was unblinded. Upon unblinding placebo subjects who received blinded treatment had an option to receive unblinded treatment with siltuximab. Subjects who discontinued or completed treatment period up to Week 48 and who consented to enter follow-up period were continued to be followed up during the course of follow-up period (up to 3 months after last study drug intake) wherein subjects were followed until death, lost to follow-up, withdrawal of consent, death of 50% of subjects, or end of the study, whichever occurred earlier.

Reporting group title	Placebo + Best Supportive Care (BSC)

Reporting group description:

Subjects received placebo as a 1-hour IV infusion every 3 weeks along with BSC until treatment failure, discontinuation of treatment, withdrawal from study, or until 48 weeks after last subject started study treatment, whichever occurred earlier. If a subject had documented treatment failure and wished to continue treatment, the subject's treatment assignment was unblinded. Upon unblinding placebo subjects who received blinded treatment had an option to receive unblinded treatment with siltuximab. Subjects who discontinued or completed treatment period up to Week 48 and who consented to enter follow-up period were continued to be followed up during the course of follow-up period (up to 3 months after last study drug intake) wherein subjects were followed until death, lost to follow-up, withdrawal of consent, death of 50% of subjects, or end of the study, whichever occurred earlier.

Reporting group title	Siltuximab + Best Supportive Care (BSC)

Reporting group description:

Subjects received siltuximab 11 mg/kg as a 1-hour IV infusion every 3 weeks along with BSC until treatment failure, discontinuation of treatment, withdrawal from study, or until 48 weeks after last subject started study treatment, whichever occurred earlier. Subjects who discontinued treatment for any reason completed End-of-Treatment (EOT) Visit and entered Follow-up Period. If a subject had documented treatment failure and wished to continue treatment, subject's treatment assignment was to be unblinded. Upon unblinding, if subejcts assigned to siltuximab, study treatment was to be discontinued, and the subject was to complete EOT Visit and enter Follow-up Period (up to 3 months after last study drug intake) wherein subjects were not received any study treatment and were followed until death, lost to follow up, withdrawal of consent, death of 50% of subjects, or end of the study, whichever occurred earlier.

Reporting group title	Placebo + Best Supportive Care (BSC)

Reporting group description:

Subjects received placebo as a 1-hour IV infusion every 3 weeks along with BSC until treatment failure, discontinuation of treatment, withdrawal from study, or until 48 weeks after last subject started study treatment, whichever occurred earlier. If a subject had documented treatment failure and wished to continue treatment, the subject's treatment assignment was unblinded. Upon unblinding placebo subjects who received blinded treatment had an option to receive unblinded treatment with siltuximab. Subjects who discontinued or completed treatment period up to Week 48 and who consented to enter follow-up period were continued to be followed up during the course of follow-up period (up to 3 months after last study drug intake) wherein subjects were followed until death, lost to follow-up, withdrawal of consent, death of 50% of subjects, or end of the study, whichever occurred earlier.

Primary: Percentage of Subjects Who Achieved Durable Tumor and Symptomatic Response - by Independent Radiology Review

End point title	Percentage of Subjects Who Achieved Durable Tumor and Symptomatic Response - by Independent Radiology Review

End point description:

Durable tumor and symptomatic response is complete response (CR) + partial response (PR). CR: complete disappearance of all measurable and evaluable disease (eg, pleural effusion) and resolution of baseline symptoms attributed to multicentric Castleman's disease, sustained for at least 18 weeks. PR: >=50 percent decrease in sum of the product of the diameters of indicator lesion(s), with at least stable disease in all other evaluable disease in the absence of treatment failure sustained for at least 18 weeks. The statistical analysis shows difference in symptomatic response rate (siltuximab+best supportive care [BSC] minus Placebo+BSC). Intent-to-treat (ITT) population: all randomized subjects.

End point type	Primary

End point timeframe:

From Day 1 of Cycle 1 of treatment with study medication until treatment failure or discontinuation of treatment or withdrawal from study, or up to 48 weeks after last subject started study medication (approximately 3 years), whichever occurred earlier

End point values	Siltuximab + Best Supportive Care (BSC)	Placebo + Best Supportive Care (BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	26		
Units: Percentage of subjects				
number (not applicable)	34	0		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Best Supportive Care (BSC) v Siltuximab + Best Supportive Care (BSC)
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in the response rate
Point estimate	34
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.1
upper limit	54.8

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo + Best Supportive Care (BSC) v Siltuximab + Best Supportive Care (BSC)
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Fisher exact
Parameter estimate	difference in the response rate
Point estimate	34
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.1
upper limit	54.8

Secondary: Median Duration of Tumor and Symptomatic Response - by Independent Radiology Review

End point title	Median Duration of Tumor and Symptomatic Response - by Independent Radiology Review

End point description:

Duration of tumor and symptomatic response is defined as time from first documentation of tumor and symptomatic response (CR or PR) to treatment failure. Whenever possible, treatment failure documented by the appearance of new lesions should be confirmed by histologic examination of the new lesions. Symptomatic response is complete response (CR) + partial response (PR). CR: complete disappearance of all measurable and evaluable disease (eg, pleural effusion) and resolution of baseline symptoms attributed to multicentric Castleman's disease, sustained for at least 18 weeks. PR: >=50 percent decrease in sum of the product of the diameters of indicator lesion(s), with at least stable disease in all other evaluable disease in the absence of treatment failure sustained for at least 18 weeks. Population analyzed included all randomized subjects who achieved durable tumor and symptomatic response during blinded treatment period as per independent review.

End point type	Secondary

End point timeframe:

From the date when durable tumour and symptomatic response is achieved until treatment failure, as assessed until 48 weeks after the last subject started study treatment (approximately 3 years)

End point values	Siltuximab + Best Supportive Care (BSC)	Placebo + Best Supportive Care (BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	0[1]		
Units: Days				
median (full range (min-max))	383.0 (232 to 676)	(to)		

Notes:

[1] - Number of Subjects Analyzed were 0 because none of the subject showed a response.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Complete Response (CR) + Partial Response (PR) (Tumor Response Rate) - by Independent Radiology Review

End point title	Percentage of Subjects Who Achieved Complete Response (CR) + Partial Response (PR) (Tumor Response Rate) - by Independent Radiology Review

End point description:

Overall tumor response is CR + PR assessed according to Cheson criteria. CR: complete disappearance of all measurable and evaluable disease (eg, pleural effusion). PR: a >=50 percent decrease in sum of the product of the diameters of index lesion(s), with at least stable disease in all other evaluable disease. Statistical analysis shows difference of overall response rates (siltuximab+best supportive care [BSC] minus Placebo+BSC). Response-evaluable Population included subjects who received at least 1 administration of siltuximab/placebo and had at least 1 post-baseline radiologic disease evaluation.

End point type	Secondary

End point timeframe:

From Day 1 of Cycle 1 until the date when durable tumour and symptomatic response is achieved, as assessed up to 48 weeks after the last subject started study treatment (approximately 3 years)

End point values	Siltuximab + Best Supportive Care (BSC)	Placebo + Best Supportive Care (BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	26		
Units: Percentage of subjects				
number (not applicable)	37.7	3.8		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Siltuximab + Best Supportive Care (BSC) v Placebo + Best Supportive Care (BSC)
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in overall response rates
Point estimate	33.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.1
upper limit	54.8

Secondary: Median Duration of Tumor Response - by Independent Radiology Review

End point title	Median Duration of Tumor Response - by Independent Radiology Review

End point description:

Duration of tumor response is defined as time from first documentation of tumor response to tumor progression. Tumour response is complete response (CR) + partial response (PR) as assessed according to Cheson criteria. CR: complete disappearance of all measurable and evaluable disease (eg, pleural effusion). PR: a >=50 percent decrease in sum of the product of the diameters of index lesion(s), with at least stable disease in all other evaluable disease. Statistical analysis shows difference of overall response rates (siltuximab+best supportive care [BSC] minus Placebo+BSC). Population analyzed included all randomized subjects who achieved tumor response during blinded treatment period as per independent review.

End point type	Secondary

End point timeframe:

From the date when tumour response is achieved until tumour progression, as assessed up to 48 weeks after the last subject started study treatment (approximately 3 years)

End point values	Siltuximab + Best Supportive Care (BSC)	Placebo + Best Supportive Care (BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	1		
Units: Days				
median (full range (min-max))	356.0 (55 to 674)	70.0 (70 to 70)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure

End point title	Time to Treatment Failure

End point description:

Time to treatment failure was defined as the time from randomization until the subjects fails treatment. Treatment failure was defined as any of the following: a sustained increase from baseline in disease related symptoms >=Grade 2 persisting for at least 3 weeks despite BSC; onset of any new disease related Grade 3 or higher symptom despite BSC; sustained (ie, at least 3 weeks) deterioration in performance status (increase from baseline in ECOG Performance Status by more than 1 point) despite BSC; radiologic progression, as per Cheson criteria; Initiation of any other therapy intended to treat multicentric Castleman’s disease ie, prohibited treatments. ITT population included all randomized subjects. Here, 99999 in siltuximab arm signifies median time to treatment failure that was not estimable and in placebo arm it signifies upper limit that was not estimable due to insufficient number of subjects with event.

End point type	Secondary

End point timeframe:

From the date of randomization until a subject fails treatment, as assessed up to 48 weeks after the last subject started study treatment (approximately 3 years), whichever occurred earlier

End point values	Siltuximab + Best Supportive Care (BSC)	Placebo + Best Supportive Care (BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	26		
Units: Days				
median (confidence interval 95%)	99999 (378 to 99999)	134.0 (85 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Siltuximab + Best Supportive Care (BSC) v Placebo + Best Supportive Care (BSC)
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0084
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.418
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.214
upper limit	0.815

Secondary: Percentage of Subjects Who Achieved Greater Than or Equal to (>=) 15 g/L Hemoglobin at Week 13 (Hemoglobin Response Rate)

End point title	Percentage of Subjects Who Achieved Greater Than or Equal to (>=) 15 g/L Hemoglobin at Week 13 (Hemoglobin Response Rate)

End point description:

Hemoglobin response rate is defined as percentage of subjects who achieved >= 15 g/L hemoglobin at Week 13. Hemoglobin response-evaluable population: subjects who received at least 1 siltuximab/placebo administration and have a baseline hemoglobin that is below the lower limit of normal as per local laboratory specifications (within 2 weeks before starting treatment) and at least 1 postbaseline hemoglobin evaluation.

End point type	Secondary

End point timeframe:

Week 13

End point values	Siltuximab + Best Supportive Care (BSC)	Placebo + Best Supportive Care (BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	11		
Units: Percentage of subjects				
number (not applicable)	61.3	0		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Siltuximab + Best Supportive Care (BSC) v Placebo + Best Supportive Care (BSC)
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference of hemoglobin response rates
Point estimate	61.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.3
upper limit	85.1

Secondary: Percentage of Subjects Who Achieved >= 20 g/L Hemoglobin at Week 13 (Hemoglobin Response Rate)

End point title	Percentage of Subjects Who Achieved >= 20 g/L Hemoglobin at Week 13 (Hemoglobin Response Rate)

End point description:

Hemoglobin response rate is defined as percentage of subjects who achieved >= 20 g/L hemoglobin at Week 13. Hemoglobin response-evaluable population: subjects who received at least 1 siltuximab/placebo administration and have a baseline hemoglobin that is below the lower limit of normal as per local laboratory specifications (within 2 weeks before starting treatment) and at least 1 post-baseline hemoglobin evaluation.

End point type	Secondary

End point timeframe:

Week 13

End point values	Siltuximab + Best Supportive Care (BSC)	Placebo + Best Supportive Care (BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	11		
Units: Percentage of subjects				
number (not applicable)	41.9	0		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Siltuximab + Best Supportive Care (BSC) v Placebo + Best Supportive Care (BSC)
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0195
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference of hemoglobin response rates
Point estimate	41.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.8
upper limit	70.7

Secondary: Percentage of Subjects Who Discontinued Corticosteroids

End point title	Percentage of Subjects Who Discontinued Corticosteroids

End point description:

Percentage of subjects who discontinued corticosteroids during blinded treatment period and who were dependent on corticosteroids at baseline (Day 1 of Cycle 1). Population analyzed included all randomized subjects who were dependent on corticosteroids at baseline.

End point type	Secondary

End point timeframe:

From Day 1 of Cycle 1 until 48 weeks after the after the last subject started study treatment (approximately 3 years)

End point values	Siltuximab + Best Supportive Care (BSC)	Placebo + Best Supportive Care (BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	9		
Units: Percentage of subjects				
number (not applicable)	30.8	11.1		

Statistical analyses

No statistical analyses for this end point

Secondary: 6-Year Survival Rate

End point title	6-Year Survival Rate

End point description:

Overall survival was defined as percent chance of survival of subjects who were still alive at 6 years from time of first study treatment was analyzed. Safety Analysis set included all subjects who received at least 1 dose of study agent were included in the safety analysis.

End point type	Secondary

End point timeframe:

until 6 years

End point values	Siltuximab + Best Supportive Care (BSC)	Placebo + Best Supportive Care (BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	26		
Units: Percent chance of survival				
median (confidence interval 95%)	86.3 (71.9 to 93.6)	79.5 (57.5 to 91.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time Required to Achieve >=1 Point Decrease in the Multicentric Castleman's Disease Symptom Scale (MCD-SS) Score From Baseline

End point title	Median Time Required to Achieve >=1 Point Decrease in the Multicentric Castleman's Disease Symptom Scale (MCD-SS) Score From Baseline

End point description:

A patient-reported symptom scale. Symptom presence/absence and severity are noted on an anchor-based numeric scale. Scores range from 1 (very mild) to 5 (very severe). Intent-to-treat (ITT) population included all randomized subjects. Here, 99999 signifies that upper limit was not estimable due to insufficient number of subjects with event.

End point type	Secondary

End point timeframe:

From Day 1 of Cycle 1 (baseline) until 48 weeks after the last subject started study treatment (approximately 3 years)

End point values	Siltuximab + Best Supportive Care (BSC)	Placebo + Best Supportive Care (BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	26		
Units: Days				
median (full range (min-max))	85.0 (22 to 379)	262.0 (40 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time Required to Achieve >=3-point Increase in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Scores From Baseline

End point title	Median Time Required to Achieve >=3-point Increase in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Scores From Baseline

End point description:

The FACIT-F, a 13-item instrument, was designed to measure patient-reported fatigue. It is one of the suite of FACIT instruments developed for outcomes in cancer. Concepts measured in the scale include tiredness, weakness, and difficulty conducting usual functional activities or social interaction due to fatigue. Response options range from "not at all" (0) to "very much" (4), and yield a summary score. Total FACIT-F score is the sum of 13 items, ranging from 0 (not at all) to 52 (very much). Higher scores represent better outcomes. Intent-to-treat (ITT) population included all randomized subjects.

End point type	Secondary

End point timeframe:

From Day 1 of Cycle 1 (baseline) until 48 weeks after the last subject started study treatment (approximately 3 years)

End point values	Siltuximab + Best Supportive Care (BSC)	Placebo + Best Supportive Care (BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	26		
Units: Days				
median (confidence interval 95%)	15 (8 to 23)	22 (8 to 64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time Required to Achieve >=5-point Increase in the Short-Form-36 (SF-36) Physical Component Summary (PCS) Scores From Baseline

End point title	Median Time Required to Achieve >=5-point Increase in the Short-Form-36 (SF-36) Physical Component Summary (PCS) Scores From Baseline

End point description:

SF-36 is a questionnaire and PCS is a part of subscale assessing physical functioning, role-physical, bodily pain, and general health. The scores range from 0 (worst score) to 100 (best score), with a higher score indicating better quality of life. Intent-to-treat (ITT) population included all randomized subjects. Here, 99999 in siltuximab arm signifies that the upper limit was not estimable due to insufficient number of subjects with event while in placebo arm signifies median time was not estimable due to insufficient number of subjects with event.

End point type	Secondary

End point timeframe:

From Day 1 of Cycle 1 (baseline) until 48 weeks after the last subject started study treatment (approximately 3 years)

End point values	Siltuximab + Best Supportive Care (BSC)	Placebo + Best Supportive Care (BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	26		
Units: Days				
median (confidence interval 95%)	420 (106 to 99999)	99999 (169 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 7 years

Adverse event reporting additional description:

Safety Analysis set included, subjects who received at least 1 dose of study drug in blinded and unblinded treatment until 48 weeks after last subject started study treatment (approximately 3 years). Follow-up analysis set included subjects who continued in study from Week 48 till end-of-study (5 years after last subject started study treatment).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Placebo + Best Supportive Care (BSC) (Blinded)

Reporting group description:

Subjects received placebo as a 1-hour intravenous infusion every 3 weeks along with BSC until treatment failure, discontinuation of treatment, withdrawal from the study, or until 48 weeks after the last subject started study treatment, whichever occurred earlier. Subjects who discontinued or completed treatment period up to Week 48 and who consented to enter follow-up period were continued to be followed up during the course of follow-up period.

Reporting group title	Siltuximab + Best Supportive Care (BSC) (Blinded)

Reporting group description:

Subjects received siltuximab 11mg/kg as a 1-hour intravenous infusion every 3 weeks along with BSC until treatment failure, discontinuation of treatment, withdrawal from the study, or until 48 weeks after the last subject started study treatment, whichever occurred earlier. Subjects who discontinued treatment for any reason completed the end-of-treatment visit and entered the follow-up period.

Reporting group title	Siltuximab + Best Supportive Care (BSC) (Unblinded)

Reporting group description:

Subjects who had documented treatment failure and wished to continue treatment, their treatment assignment was unblinded. Upon unblinding placebo subjects who received blinded treatment had an option to receive unblinded treatment with siltuximab during the unblinded treatment period.

Reporting group title	Placebo + BSC (Follow-up Period)

Reporting group description:

No study treatment was administered during the follow-up period (up to 3 months after last study agent administration [placebo as a 1 hour IV infusion every 3 weeks along with BSC]) and subjects were followed until death, lost to follow up, withdrawal of consent, death of 50 % of subjects, or the end of the study, whichever occurred earlier.

Reporting group title	Siltuximab + BSC (Follow-up Period)

Reporting group description:

No study treatment was administered during the follow-up period (up to 3 months after last study agent administration [siltuximab 11mg/kg as a 1 hour IV infusion every 3 weeks along with]) and subjects were followed until death, lost to follow up, withdrawal of consent, death of 50 % of subjects, or the end of the study, whichever occurred earlier.

Serious adverse events	Placebo + Best Supportive Care (BSC) (Blinded)	Siltuximab + Best Supportive Care (BSC) (Blinded)	Siltuximab + Best Supportive Care (BSC) (Unblinded)
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 26 (26.92%)	12 / 53 (22.64%)	4 / 13 (30.77%)
number of deaths (all causes)	5	6	0
number of deaths resulting from			

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Poems Syndrome			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
T-Cell Lymphoma			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive Crisis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Pain Management			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema Peripheral			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Dyspnoea			
subjects affected / exposed	2 / 26 (7.69%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	3 / 26 (11.54%)	1 / 53 (1.89%)	2 / 13 (15.38%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Mycobacterium Test			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia Fracture			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound Secretion			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac Failure Congestive			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Eye disorders			
Vitreous Haemorrhage			

subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical Hernia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis Chronic			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Colic			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteral Disorder			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscle Spasms			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal Abscess			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 26 (11.54%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo + BSC (Follow-up Period)	Siltuximab + BSC (Follow-up Period)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	3 / 14 (21.43%)	
number of deaths (all causes)	1	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Poems Syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
T-Cell Lymphoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive Crisis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Pain Management			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema Peripheral			

subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Mycobacterium Test			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia Fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Secretion			

subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac Failure Congestive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vitreous Haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical Hernia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis Chronic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Dysuria			

subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Colic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteral Disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle Spasms			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal Abscess			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung Infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Best Supportive Care (BSC) (Blinded)	Siltuximab + Best Supportive Care (BSC) (Blinded)	Siltuximab + Best Supportive Care (BSC) (Unblinded)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 26 (96.15%)	53 / 53 (100.00%)	13 / 13 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour Pain			
subjects affected / exposed	4 / 26 (15.38%)	4 / 53 (7.55%)	2 / 13 (15.38%)
occurrences (all)	6	6	4
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 26 (7.69%)	2 / 53 (3.77%)	2 / 13 (15.38%)
occurrences (all)	2	2	2
Haemorrhage			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Hypertension			
subjects affected / exposed	3 / 26 (11.54%)	4 / 53 (7.55%)	3 / 13 (23.08%)
occurrences (all)	5	7	5
General disorders and administration site conditions			

Chest Discomfort			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Chest Pain			
subjects affected / exposed	2 / 26 (7.69%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	1
Chills			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	2
Face Oedema			
subjects affected / exposed	1 / 26 (3.85%)	6 / 53 (11.32%)	1 / 13 (7.69%)
occurrences (all)	1	7	2
Fatigue			
subjects affected / exposed	14 / 26 (53.85%)	18 / 53 (33.96%)	8 / 13 (61.54%)
occurrences (all)	26	38	17
Generalised Oedema			
subjects affected / exposed	4 / 26 (15.38%)	7 / 53 (13.21%)	2 / 13 (15.38%)
occurrences (all)	4	9	3
Influenza Like Illness			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Infusion Site Extravasation			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Localised Oedema			
subjects affected / exposed	3 / 26 (11.54%)	11 / 53 (20.75%)	2 / 13 (15.38%)
occurrences (all)	4	24	5
Malaise			
subjects affected / exposed	7 / 26 (26.92%)	15 / 53 (28.30%)	6 / 13 (46.15%)
occurrences (all)	11	20	14
Oedema Peripheral			
subjects affected / exposed	8 / 26 (30.77%)	19 / 53 (35.85%)	4 / 13 (30.77%)
occurrences (all)	10	33	6
Pain			
subjects affected / exposed	2 / 26 (7.69%)	3 / 53 (5.66%)	1 / 13 (7.69%)
occurrences (all)	2	3	1

Pyrexia			
subjects affected / exposed	4 / 26 (15.38%)	6 / 53 (11.32%)	2 / 13 (15.38%)
occurrences (all)	6	7	3
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	1 / 26 (3.85%)	2 / 53 (3.77%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	2
Oedema Genital			
subjects affected / exposed	2 / 26 (7.69%)	3 / 53 (5.66%)	0 / 13 (0.00%)
occurrences (all)	2	3	0
Pelvic Pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	5	0	5
Scrotal Swelling			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 26 (30.77%)	8 / 53 (15.09%)	3 / 13 (23.08%)
occurrences (all)	12	14	3
Dyspnoea			
subjects affected / exposed	9 / 26 (34.62%)	13 / 53 (24.53%)	4 / 13 (30.77%)
occurrences (all)	12	18	6
Epistaxis			
subjects affected / exposed	1 / 26 (3.85%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	1	1	2
Nasal Inflammation			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Oropharyngeal Pain			
subjects affected / exposed	2 / 26 (7.69%)	4 / 53 (7.55%)	2 / 13 (15.38%)
occurrences (all)	2	5	2

Pleural Effusion			
subjects affected / exposed	5 / 26 (19.23%)	2 / 53 (3.77%)	2 / 13 (15.38%)
occurrences (all)	5	2	3
Productive Cough			
subjects affected / exposed	1 / 26 (3.85%)	2 / 53 (3.77%)	0 / 13 (0.00%)
occurrences (all)	1	2	0
Wheezing			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 26 (7.69%)	5 / 53 (9.43%)	0 / 13 (0.00%)
occurrences (all)	2	6	0
Investigations			
Blood Albumin Decreased			
subjects affected / exposed	3 / 26 (11.54%)	1 / 53 (1.89%)	2 / 13 (15.38%)
occurrences (all)	5	1	4
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Blood Folate Decreased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Blood Iron Decreased			
subjects affected / exposed	1 / 26 (3.85%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	2	1	2
Blood Phosphorus Increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Haemoglobin Increased			
subjects affected / exposed	0 / 26 (0.00%)	2 / 53 (3.77%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Iron Binding Capacity Total Decreased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Iron Binding Capacity Unsaturated			

Decreased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	2
Platelet Count Increased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Protein Total Decreased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Protein Total Increased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	4
Protein Urine Present			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Reticulocyte Count Decreased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Reticulocyte Percentage Decreased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Serum Ferritin Decreased			
subjects affected / exposed	0 / 26 (0.00%)	3 / 53 (5.66%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Vitamin B12 Decreased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Weight Decreased			
subjects affected / exposed	7 / 26 (26.92%)	4 / 53 (7.55%)	3 / 13 (23.08%)
occurrences (all)	9	9	5
Weight Increased			
subjects affected / exposed	0 / 26 (0.00%)	11 / 53 (20.75%)	0 / 13 (0.00%)
occurrences (all)	0	20	0
Injury, poisoning and procedural complications			

Arthropod Bite			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	2
Contusion			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Head Injury			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Ligament Sprain			
subjects affected / exposed	2 / 26 (7.69%)	0 / 53 (0.00%)	2 / 13 (15.38%)
occurrences (all)	2	0	2
Post-Traumatic Pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Procedural Nausea			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Road Traffic Accident			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	2
Skin Abrasion			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Wound			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	4	0	4
Wound Complication			
subjects affected / exposed	1 / 26 (3.85%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	1	1	2
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 26 (3.85%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
Ventricular Extrasystoles			

subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 26 (7.69%)	6 / 53 (11.32%)	0 / 13 (0.00%)
occurrences (all)	4	8	0
Headache			
subjects affected / exposed	1 / 26 (3.85%)	6 / 53 (11.32%)	0 / 13 (0.00%)
occurrences (all)	1	8	0
Peripheral Motor Neuropathy			
subjects affected / exposed	4 / 26 (15.38%)	6 / 53 (11.32%)	2 / 13 (15.38%)
occurrences (all)	6	8	4
Peripheral Sensory Neuropathy			
subjects affected / exposed	7 / 26 (26.92%)	13 / 53 (24.53%)	5 / 13 (38.46%)
occurrences (all)	12	28	11
Somnolence			
subjects affected / exposed	1 / 26 (3.85%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Syncope			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 26 (19.23%)	5 / 53 (9.43%)	4 / 13 (30.77%)
occurrences (all)	14	6	13
Coagulopathy			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Leukocytosis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	2
Leukopenia			
subjects affected / exposed	2 / 26 (7.69%)	3 / 53 (5.66%)	1 / 13 (7.69%)
occurrences (all)	3	14	2
Lymph Node Pain			

subjects affected / exposed	1 / 26 (3.85%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
Lymphopenia			
subjects affected / exposed	3 / 26 (11.54%)	0 / 53 (0.00%)	2 / 13 (15.38%)
occurrences (all)	13	0	13
Monocytosis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	2
Neutropenia			
subjects affected / exposed	3 / 26 (11.54%)	7 / 53 (13.21%)	2 / 13 (15.38%)
occurrences (all)	8	26	6
Neutrophilia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	2
Splenomegaly			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	2 / 26 (7.69%)	8 / 53 (15.09%)	1 / 13 (7.69%)
occurrences (all)	6	16	6
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	2 / 26 (7.69%)	2 / 53 (3.77%)	2 / 13 (15.38%)
occurrences (all)	2	4	2
Eye disorders			
Idiopathic Orbital Inflammation			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Noninfective Conjunctivitis			
subjects affected / exposed	2 / 26 (7.69%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	2	2	2
Periorbital Oedema			

subjects affected / exposed	2 / 26 (7.69%)	3 / 53 (5.66%)	2 / 13 (15.38%)
occurrences (all)	2	5	2
Vision Blurred			
subjects affected / exposed	1 / 26 (3.85%)	3 / 53 (5.66%)	1 / 13 (7.69%)
occurrences (all)	1	3	1
Visual Acuity Reduced			
subjects affected / exposed	0 / 26 (0.00%)	2 / 53 (3.77%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	1 / 26 (3.85%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	1	1	2
Abdominal Distension			
subjects affected / exposed	2 / 26 (7.69%)	4 / 53 (7.55%)	1 / 13 (7.69%)
occurrences (all)	2	4	1
Abdominal Pain			
subjects affected / exposed	2 / 26 (7.69%)	8 / 53 (15.09%)	1 / 13 (7.69%)
occurrences (all)	3	10	1
Abdominal Pain Lower			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	2
Abdominal Pain Upper			
subjects affected / exposed	2 / 26 (7.69%)	5 / 53 (9.43%)	1 / 13 (7.69%)
occurrences (all)	8	6	7
Aphthous Ulcer			
subjects affected / exposed	1 / 26 (3.85%)	4 / 53 (7.55%)	1 / 13 (7.69%)
occurrences (all)	1	5	1
Ascites			
subjects affected / exposed	3 / 26 (11.54%)	3 / 53 (5.66%)	1 / 13 (7.69%)
occurrences (all)	5	5	6
Constipation			
subjects affected / exposed	2 / 26 (7.69%)	6 / 53 (11.32%)	1 / 13 (7.69%)
occurrences (all)	2	7	1
Diarrhoea			
subjects affected / exposed	8 / 26 (30.77%)	13 / 53 (24.53%)	4 / 13 (30.77%)
occurrences (all)	16	18	10

Dyspepsia			
subjects affected / exposed	4 / 26 (15.38%)	2 / 53 (3.77%)	3 / 13 (23.08%)
occurrences (all)	4	2	3
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 26 (0.00%)	4 / 53 (7.55%)	0 / 13 (0.00%)
occurrences (all)	0	6	0
Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Ileus Paralytic			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	7 / 26 (26.92%)	5 / 53 (9.43%)	3 / 13 (23.08%)
occurrences (all)	9	10	3
Oesophagitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Tongue Coated			
subjects affected / exposed	1 / 26 (3.85%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
Tongue Ulceration			
subjects affected / exposed	2 / 26 (7.69%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	9	1	8
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	5 / 26 (19.23%)	6 / 53 (11.32%)	3 / 13 (23.08%)
occurrences (all)	7	8	4
Hepatobiliary disorders			
Hepatic Function Abnormal			
subjects affected / exposed	3 / 26 (11.54%)	2 / 53 (3.77%)	3 / 13 (23.08%)
occurrences (all)	4	5	4
Skin and subcutaneous tissue disorders			

Blister			
subjects affected / exposed	1 / 26 (3.85%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
Dermatitis Acneiform			
subjects affected / exposed	2 / 26 (7.69%)	4 / 53 (7.55%)	2 / 13 (15.38%)
occurrences (all)	2	8	2
Dry Skin			
subjects affected / exposed	0 / 26 (0.00%)	4 / 53 (7.55%)	0 / 13 (0.00%)
occurrences (all)	0	4	0
Eczema			
subjects affected / exposed	1 / 26 (3.85%)	5 / 53 (9.43%)	1 / 13 (7.69%)
occurrences (all)	1	6	1
Erythema			
subjects affected / exposed	2 / 26 (7.69%)	2 / 53 (3.77%)	2 / 13 (15.38%)
occurrences (all)	3	3	3
Hyperhidrosis			
subjects affected / exposed	7 / 26 (26.92%)	10 / 53 (18.87%)	5 / 13 (38.46%)
occurrences (all)	9	20	9
Night Sweats			
subjects affected / exposed	4 / 26 (15.38%)	9 / 53 (16.98%)	4 / 13 (30.77%)
occurrences (all)	6	15	7
Pruritus			
subjects affected / exposed	6 / 26 (23.08%)	22 / 53 (41.51%)	4 / 13 (30.77%)
occurrences (all)	11	47	10
Rash			
subjects affected / exposed	1 / 26 (3.85%)	7 / 53 (13.21%)	0 / 13 (0.00%)
occurrences (all)	1	8	0
Rash Maculo-Papular			
subjects affected / exposed	5 / 26 (19.23%)	18 / 53 (33.96%)	3 / 13 (23.08%)
occurrences (all)	9	37	11
Rash Pruritic			
subjects affected / exposed	1 / 26 (3.85%)	2 / 53 (3.77%)	1 / 13 (7.69%)
occurrences (all)	3	2	3
Skin Hyperpigmentation			
subjects affected / exposed	0 / 26 (0.00%)	5 / 53 (9.43%)	0 / 13 (0.00%)
occurrences (all)	0	5	0

Skin Induration			
subjects affected / exposed	2 / 26 (7.69%)	2 / 53 (3.77%)	1 / 13 (7.69%)
occurrences (all)	2	2	1
Skin Ulcer			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	2 / 26 (7.69%)	2 / 53 (3.77%)	1 / 13 (7.69%)
occurrences (all)	2	4	2
Haematuria			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	2 / 26 (7.69%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	2	1	2
Polyuria			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Proteinuria			
subjects affected / exposed	1 / 26 (3.85%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	2	1	2
Renal Impairment			
subjects affected / exposed	2 / 26 (7.69%)	4 / 53 (7.55%)	2 / 13 (15.38%)
occurrences (all)	5	9	6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 26 (19.23%)	4 / 53 (7.55%)	4 / 13 (30.77%)
occurrences (all)	6	5	5
Arthritis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Back Pain			
subjects affected / exposed	6 / 26 (23.08%)	4 / 53 (7.55%)	4 / 13 (30.77%)
occurrences (all)	8	4	7
Chondropathy			

subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Joint Stiffness			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Muscle Spasms			
subjects affected / exposed	2 / 26 (7.69%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	2	1	1
Muscular Weakness			
subjects affected / exposed	0 / 26 (0.00%)	3 / 53 (5.66%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal Pain			
subjects affected / exposed	2 / 26 (7.69%)	3 / 53 (5.66%)	2 / 13 (15.38%)
occurrences (all)	3	3	3
Myalgia			
subjects affected / exposed	3 / 26 (11.54%)	2 / 53 (3.77%)	3 / 13 (23.08%)
occurrences (all)	7	2	11
Pain in Extremity			
subjects affected / exposed	2 / 26 (7.69%)	1 / 53 (1.89%)	2 / 13 (15.38%)
occurrences (all)	2	4	3
Synovitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 26 (3.85%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	2	2	2
Folliculitis			
subjects affected / exposed	2 / 26 (7.69%)	1 / 53 (1.89%)	2 / 13 (15.38%)
occurrences (all)	2	2	2
Gastroenteritis			
subjects affected / exposed	3 / 26 (11.54%)	4 / 53 (7.55%)	1 / 13 (7.69%)
occurrences (all)	3	4	1
Herpes Virus Infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1

Herpes Zoster			
subjects affected / exposed	1 / 26 (3.85%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 26 (0.00%)	2 / 53 (3.77%)	0 / 13 (0.00%)
occurrences (all)	0	6	0
Nasopharyngitis			
subjects affected / exposed	1 / 26 (3.85%)	9 / 53 (16.98%)	1 / 13 (7.69%)
occurrences (all)	1	10	2
Oral Candidiasis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Pharyngitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Pneumonia			
subjects affected / exposed	0 / 26 (0.00%)	2 / 53 (3.77%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Rash Pustular			
subjects affected / exposed	2 / 26 (7.69%)	4 / 53 (7.55%)	2 / 13 (15.38%)
occurrences (all)	3	5	3
Respiratory Tract Infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Skin Infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Tonsillitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Upper Respiratory Tract Infection			
subjects affected / exposed	6 / 26 (23.08%)	20 / 53 (37.74%)	4 / 13 (30.77%)
occurrences (all)	12	31	11
Urinary Tract Infection			
subjects affected / exposed	0 / 26 (0.00%)	4 / 53 (7.55%)	0 / 13 (0.00%)
occurrences (all)	0	4	0

Viral Infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	7 / 26 (26.92%)	9 / 53 (16.98%)	4 / 13 (30.77%)
occurrences (all)	7	13	6
Enzyme Abnormality			
subjects affected / exposed	4 / 26 (15.38%)	1 / 53 (1.89%)	4 / 13 (30.77%)
occurrences (all)	6	2	7
Fluid Overload			
subjects affected / exposed	1 / 26 (3.85%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
Gout			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Hypercholesterolaemia			
subjects affected / exposed	0 / 26 (0.00%)	3 / 53 (5.66%)	0 / 13 (0.00%)
occurrences (all)	0	7	0
Hyperglycaemia			
subjects affected / exposed	2 / 26 (7.69%)	1 / 53 (1.89%)	1 / 13 (7.69%)
occurrences (all)	2	1	1
Hyperkalaemia			
subjects affected / exposed	0 / 26 (0.00%)	3 / 53 (5.66%)	0 / 13 (0.00%)
occurrences (all)	0	10	0
Hyperphosphataemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 53 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Hypertriglyceridaemia			
subjects affected / exposed	2 / 26 (7.69%)	7 / 53 (13.21%)	1 / 13 (7.69%)
occurrences (all)	2	15	1
Hyperuricaemia			
subjects affected / exposed	1 / 26 (3.85%)	7 / 53 (13.21%)	1 / 13 (7.69%)
occurrences (all)	3	12	6
Hypoalbuminaemia			

subjects affected / exposed	2 / 26 (7.69%)	2 / 53 (3.77%)	1 / 13 (7.69%)
occurrences (all)	2	5	2
Hypocalcaemia			
subjects affected / exposed	4 / 26 (15.38%)	3 / 53 (5.66%)	2 / 13 (15.38%)
occurrences (all)	4	3	2
Hypocholesterolaemia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	2 / 26 (7.69%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	3	1	0
Hypokalaemia			
subjects affected / exposed	3 / 26 (11.54%)	6 / 53 (11.32%)	1 / 13 (7.69%)
occurrences (all)	5	6	1
Hyponatraemia			
subjects affected / exposed	1 / 26 (3.85%)	1 / 53 (1.89%)	0 / 13 (0.00%)
occurrences (all)	2	1	0

Non-serious adverse events	Placebo + BSC (Follow-up Period)	Siltuximab + BSC (Follow-up Period)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	14 / 14 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour Pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Chest Discomfort			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Chest Pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Chills			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Face Oedema			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	
occurrences (all)	1	2	
Fatigue			
subjects affected / exposed	2 / 6 (33.33%)	4 / 14 (28.57%)	
occurrences (all)	4	5	
Generalised Oedema			
subjects affected / exposed	2 / 6 (33.33%)	1 / 14 (7.14%)	
occurrences (all)	2	2	
Influenza Like Illness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Infusion Site Extravasation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Localised Oedema			
subjects affected / exposed	2 / 6 (33.33%)	1 / 14 (7.14%)	
occurrences (all)	3	5	
Malaise			
subjects affected / exposed	2 / 6 (33.33%)	5 / 14 (35.71%)	
occurrences (all)	4	7	
Oedema Peripheral			
subjects affected / exposed	3 / 6 (50.00%)	5 / 14 (35.71%)	
occurrences (all)	4	9	
Pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	

Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 14 (21.43%)	
occurrences (all)	0	4	
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Oedema Genital			
subjects affected / exposed	1 / 6 (16.67%)	2 / 14 (14.29%)	
occurrences (all)	1	2	
Pelvic Pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Scrotal Swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	3 / 14 (21.43%)	
occurrences (all)	0	4	
Epistaxis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Nasal Inflammation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal Pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	

Pleural Effusion			
subjects affected / exposed	3 / 6 (50.00%)	2 / 14 (14.29%)	
occurrences (all)	3	2	
Productive Cough			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood Albumin Decreased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Blood Folate Decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Blood Iron Decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Blood Phosphorus Increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Haemoglobin Increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Iron Binding Capacity Total Decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Iron Binding Capacity Unsaturated			

Decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Platelet Count Increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Protein Total Decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Protein Total Increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Protein Urine Present			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Reticulocyte Count Decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Reticulocyte Percentage Decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Serum Ferritin Decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Vitamin B12 Decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Weight Decreased			
subjects affected / exposed	3 / 6 (50.00%)	2 / 14 (14.29%)	
occurrences (all)	3	5	
Weight Increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

Arthropod Bite			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Head Injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Ligament Sprain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Post-Traumatic Pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Procedural Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Road Traffic Accident			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Skin Abrasion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Wound			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Wound Complication			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Ventricular Extrasystoles			

subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Peripheral Motor Neuropathy			
subjects affected / exposed	2 / 6 (33.33%)	1 / 14 (7.14%)	
occurrences (all)	3	1	
Peripheral Sensory Neuropathy			
subjects affected / exposed	3 / 6 (50.00%)	3 / 14 (21.43%)	
occurrences (all)	3	3	
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 6 (33.33%)	2 / 14 (14.29%)	
occurrences (all)	3	2	
Coagulopathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Leukocytosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Leukopenia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 14 (7.14%)	
occurrences (all)	3	3	
Lymph Node Pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Lymphopenia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Monocytosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 14 (7.14%)	
occurrences (all)	4	5	
Neutrophilia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Splenomegaly			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 14 (21.43%)	
occurrences (all)	3	4	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Vertigo			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Idiopathic Orbital Inflammation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Noninfective Conjunctivitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Periorbital Oedema			

subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	3	
Vision Blurred			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Visual Acuity Reduced			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Abdominal Distension			
subjects affected / exposed	0 / 6 (0.00%)	3 / 14 (21.43%)	
occurrences (all)	0	3	
Abdominal Pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Abdominal Pain Lower			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Abdominal Pain Upper			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Aphthous Ulcer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Ascites			
subjects affected / exposed	1 / 6 (16.67%)	2 / 14 (14.29%)	
occurrences (all)	3	2	
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	2 / 6 (33.33%)	3 / 14 (21.43%)	
occurrences (all)	2	3	

Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	3	
Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Ileus Paralytic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Oesophagitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Tongue Coated			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Tongue Ulceration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Hepatobiliary disorders			
Hepatic Function Abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			

Blister			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Dermatitis Acneiform			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Dry Skin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Eczema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Hyperhidrosis			
subjects affected / exposed	2 / 6 (33.33%)	2 / 14 (14.29%)	
occurrences (all)	3	4	
Night Sweats			
subjects affected / exposed	1 / 6 (16.67%)	4 / 14 (28.57%)	
occurrences (all)	1	5	
Pruritus			
subjects affected / exposed	2 / 6 (33.33%)	3 / 14 (21.43%)	
occurrences (all)	2	5	
Rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Rash Maculo-Papular			
subjects affected / exposed	2 / 6 (33.33%)	2 / 14 (14.29%)	
occurrences (all)	5	4	
Rash Pruritic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Skin Hyperpigmentation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	

Skin Induration			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Skin Ulcer			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Polyuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Proteinuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Renal Impairment			
subjects affected / exposed	1 / 6 (16.67%)	2 / 14 (14.29%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	
occurrences (all)	1	2	
Arthritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Back Pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Chondropathy			

subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Joint Stiffness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Muscle Spasms			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Muscular Weakness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal Pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	4	0	
Pain in Extremity			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Synovitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Folliculitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Herpes Virus Infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	

Herpes Zoster				
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)		
occurrences (all)	0	0		
Lower Respiratory Tract Infection				
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)		
occurrences (all)	0	5		
Nasopharyngitis				
subjects affected / exposed	1 / 6 (16.67%)	2 / 14 (14.29%)		
occurrences (all)	1	2		
Oral Candidiasis				
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)		
occurrences (all)	0	0		
Pharyngitis				
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)		
occurrences (all)	0	0		
Pneumonia				
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)		
occurrences (all)	0	1		
Rash Pustular				
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)		
occurrences (all)	0	0		
Respiratory Tract Infection				
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)		
occurrences (all)	0	0		
Skin Infection				
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)		
occurrences (all)	0	0		
Tonsillitis				
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)		
occurrences (all)	0	1		
Upper Respiratory Tract Infection				
subjects affected / exposed	1 / 6 (16.67%)	2 / 14 (14.29%)		
occurrences (all)	1	2		
Urinary Tract Infection				
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)		
occurrences (all)	0	0		

Viral Infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	3 / 6 (50.00%)	4 / 14 (28.57%)	
occurrences (all)	3	6	
Enzyme Abnormality			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Fluid Overload			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Gout			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Hypercholesterolaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Hyperphosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	
occurrences (all)	0	0	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 14 (21.43%)	
occurrences (all)	3	5	
Hypoalbuminaemia			

subjects affected / exposed	2 / 6 (33.33%)	1 / 14 (7.14%)	
occurrences (all)	2	1	
Hypocalcaemia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 14 (21.43%)	
occurrences (all)	1	3	
Hypocholesterolaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Hypoglycaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Hypokalaemia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	
occurrences (all)	3	1	
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported