Clinical trial results:
An Open-label, Multicenter Study to Evaluate the Safety of Long-term Treatment with Siltuximab in Subjects with Multicentric Castleman's Disease

Summary

EudraCT number	2010-022837-27
Trial protocol	BE GB DE ES
Global end of trial date	02 March 2017

Results information

Result version number	v1 (current)
This version publication date	17 March 2018
First version publication date	17 March 2018

Trial information

Trial identification

Sponsor protocol code	CR018469

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01400503
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research and Development, LLC
Sponsor organisation address	Archimedesweg 29, Leiden, Netherlands, 2333CM
Public contact	Clinical Registry Group,, Janssen Research and Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group,, Janssen Research and 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	02 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the long-term safety of siltuximab in subjects with Multicentric Castleman's Disease Symptom (MCD).

Protection of trial subjects:

The safety assessments included severity of adverse events (AEs) reported throughout the study, with a focus on infections, hyperlipidemia, neutropenia, thrombocytopenia, gastrointestinal (GI) perforations, infusion-related reactions, liver enzyme abnormalities, and immunogenicity changes; clinical laboratory test values (hematology, biochemistry, and coagulation parameters); vital sign measurements; 12-lead ECG; and physical examination (including weight and height).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	China: 6
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: 3
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	60
EEA total number of subjects	11

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)	55
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects enrolled in this study CNTO328MCD2002 included subjects who were previously enrolled in study C0328T03 (NCT00412321) or CNTO328MCD2001 (NCT01024036) (either placebo or siltuximab treatment arm). A total of 60 subjects from previous MCD studies C0328T03 and CNTO328MCD2001 were found eligible to be enrolled in this study.

Period 1

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

Arms

Arm title	Siltuximab

Arm description:

Subjects received siltuximab 11 milligram per kilogram (mg/kg) as a 1-hour intravenous infusion every 3 weeks until disease progression, withdrew, experienced unacceptable toxicity,or until the 6-year data cutoff, whichever occurred first.

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 milligram per kilogram (mg/kg) as a 1-hour intravenous infusion every 3 weeks until disease progression, withdrew, experienced unacceptable toxicity,or until the 6-year data cutoff, whichever occurred first.

Number of subjects in period 1	Siltuximab
Started	60
Completed	0
Not completed	60
Consent withdrawn by subject	1
Study terminated by sponsor	58
Unspecified	1

Baseline characteristics

Reporting groups	
Reporting group title	Siltuximab
Reporting group description:	
Subjects received siltuximab 11 milligram per kilogram (mg/kg) as a 1-hour intravenous infusion every 3 weeks until disease progression, withdrew, experienced unacceptable toxicity,or until the 6-year data cutoff, whichever occurred first.	

Reporting group values	Siltuximab	Total	
Number of subjects	60	60	
Title for AgeCategorical Units: subjects			
infants and toddlers(28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	55	55	
From 65 to 84 years	5	5	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	45.1		
standard deviation	± 14.51	-	
Title for Gender Units: subjects			
Female	20	20	
Male	40	40	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	23	23	
Native Hawaiian or Other Pacific Islander	2	2	
Black or African American	3	3	
White	31	31	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	5	
Not Hispanic or Latino	55	55	
Unknown or Not Reported	0	0	
Race/Ethnicity, Customized Units: Subjects			
Asian	23	23	
Black or African American	3	3	
Hispanic or Latino	5	5	
Other	3	3	
White Non-Hispanic	26	26	

End points

End points reporting groups

Reporting group title	Siltuximab

Reporting group description:

Subjects received siltuximab 11 milligram per kilogram (mg/kg) as a 1-hour intravenous infusion every 3 weeks until disease progression, withdrew, experienced unacceptable toxicity,or until the 6-year data cutoff, whichever occurred first.

Primary: Number of Subjects with Adverse Events (AEs)

End point title	Number of Subjects with Adverse Events (AEs)[1]

End point description:

An adverse event (AE) is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. Safety analysis set included all enrolled subjects in this study.

End point type	Primary

End point timeframe:

Up to 6 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Siltuximab			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: Subjects	60			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Previously Responding Subjects who Maintained Disease Control

End point title	Percentage of Previously Responding Subjects who Maintained Disease Control

End point description:

Percentage of subjects maintaining disease control (defined as stable or better response) was defined as the percentage of previously responding subjects who had not progressed during the long-term safety extension based on investigator assessment. A worsening in any of the measures will be considered as a progression of the disease.Population included subset of safety analysis set who previously responded to siltuximab treatment ie, did not report disease progression while receiving siltuximab in study C0328T03 or CNTO328MCD2001.

End point type	Secondary

End point timeframe:

Up to 6 years

End point values	Siltuximab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percentage of subjects				
number (not applicable)	96.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Siltuximab-naive Subjects who Experienced Disease Control

End point title	Percentage of Siltuximab-naive Subjects who Experienced Disease Control

End point description:

Percentage of subjects experiencing disease control was defined as the percentage of siltuximab-naïve subjects who had stable or better response during the long-term safety extension based on investigator's judgment. Disease control was defined as stable or better response assessed by the investigators. Population included subset of safety analysis set who were previously Siltuximab-naive i.e., received placebo in study CNTO328MCD2001 and never received siltuximab prior to enrollment in

End point type	Secondary

End point timeframe:

Up to 6 years

End point values	Siltuximab			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: percentage of subjects				
number (not applicable)	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Disease Control

End point title	Duration of Disease Control

End point description:

Duration of disease control (DODC) was defined as the time from the first siltuximab administration in this study to disease progression as assessed by the investigator. Disease control was defined as stable or better response assessed by the investigators. Kaplan-Meier method was used to estimate the duration of disease control. '99999' indicates median and CI were not estimable due to insufficient number of subjects with loss of response or disease control (due to high censorship rate). Safety

analysis set included all enrolled subjects in this study.

End point type	Secondary

End point timeframe:

Up to 6 years

End point values	Siltuximab			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: years				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time between the first study siltuximab administration and death due to any cause. Kaplan-Meier method was used to estimate the overall survival. '99999' indicates median and CI were not estimable due to insufficient number of subjects with death. Safety analysis set included all enrolled subjects in this study.

End point type	Secondary

End point timeframe:

Up to 6 years

End point values	Siltuximab			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: years				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Positive for Antibodies to Siltuximab

End point title	Number of Subjects Positive for Antibodies to Siltuximab

End point description:

Serum samples were screened for antibodies binding to siltuximab and number of subjects positive for

antibodies to siltuximab was reported.Safety analysis set included all enrolled subjects in this study.

End point type	Secondary

End point timeframe:

Up to 6 years

End point values	Siltuximab			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: Subjects	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 6 years

Adverse event reporting additional description:

An AE is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. Safety analysis set included all enrolled subjects in this study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Siltuximab

Reporting group description:

Subjects received siltuximab 11 milligram per kilogram (mg/kg) as a 1-hour intravenous infusion every 3 weeks until disease progression, withdrew, experienced unacceptable toxicity,or until the 6-year data cutoff, whichever occurred first.

Serious adverse events	Siltuximab		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 60 (41.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign Neoplasm of Testis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine Leiomyoma			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Mastectomy			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast			

disorders			
Haemorrhagic Ovarian Cyst			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine Haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Avulsion Fracture			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest Injury			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Contusion			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fractured Sacrum			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ilium Fracture			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pubis Fracture			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib Fracture			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tibia Fracture			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrospinal Fluid Leakage			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Anaemia				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphadenopathy				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Polycythaemia				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Nausea				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Henoch-Schonlein Purpura				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Micturition Disorder				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary Retention				
subjects affected / exposed	2 / 60 (3.33%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back Pain				

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal Column Stenosis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parotitis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Siltuximab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 60 (96.67%)		
Vascular disorders			
Hot Flush			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	7 / 60 (11.67%)		
occurrences (all)	7		
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	18 / 60 (30.00%)		
occurrences (all)	22		
Oedema Peripheral			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	5		
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 60 (20.00%)		
occurrences (all)	13		
Dyspnoea			
subjects affected / exposed	7 / 60 (11.67%)		
occurrences (all)	11		

Epistaxis			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Nasal Congestion			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	4		
Oropharyngeal Pain			
subjects affected / exposed	7 / 60 (11.67%)		
occurrences (all)	9		
Productive Cough			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	6		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	7		
Depression			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	8		
Aspartate Aminotransferase Increased			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	7		
Blood Creatinine Increased			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	13		
Blood Fibrinogen Decreased			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Haemoglobin Increased			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	16		
Weight Increased			

subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	5		
Skin Abrasion			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	7		
Headache			
subjects affected / exposed	7 / 60 (11.67%)		
occurrences (all)	8		
Neuropathy Peripheral			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	5		
Paraesthesia			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	4		
Peripheral Sensory Neuropathy			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	9		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	5		
Neutropenia			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	36		
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	6		

Vertigo			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	7		
Eye disorders			
Cataract			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	5		
Vision Blurred			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	8 / 60 (13.33%)		
occurrences (all)	10		
Abdominal Pain Upper			
subjects affected / exposed	7 / 60 (11.67%)		
occurrences (all)	10		
Aphthous Ulcer			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	18		
Diarrhoea			
subjects affected / exposed	16 / 60 (26.67%)		
occurrences (all)	31		
Constipation			
subjects affected / exposed	11 / 60 (18.33%)		
occurrences (all)	17		
Dyspepsia			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	4		
Gastrooesophageal Reflux Disease			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	11 / 60 (18.33%)		
occurrences (all)	17		
Vomiting			

subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	10		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	4		
Eczema			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	7		
Hyperhidrosis			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	4		
Night Sweats			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	7		
Pruritus			
subjects affected / exposed	7 / 60 (11.67%)		
occurrences (all)	10		
Rash			
subjects affected / exposed	13 / 60 (21.67%)		
occurrences (all)	25		
Rash Maculo-Papular			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Urticaria			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 60 (25.00%)		
occurrences (all)	36		
Back Pain			

subjects affected / exposed	14 / 60 (23.33%)		
occurrences (all)	21		
Muscle Spasms			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Musculoskeletal Pain			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	9		
Neck Pain			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	7		
Pain in Extremity			
subjects affected / exposed	10 / 60 (16.67%)		
occurrences (all)	18		
Infections and infestations			
Cystitis			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	4		
Ear Infection			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	5		
Gastroenteritis			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	6		
Herpes Zoster			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Influenza			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	4		
Otitis Media			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		

Respiratory Tract Infection			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Pneumonia			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	5		
Rhinitis			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Sinusitis			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	10		
Urinary Tract Infection			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Upper Respiratory Tract Infection			
subjects affected / exposed	26 / 60 (43.33%)		
occurrences (all)	94		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	10 / 60 (16.67%)		
occurrences (all)	13		
Hypercholesterolaemia			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Gout			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	5		
Hypertriglyceridaemia			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2012	The overall reason for the amendment was to update the secondary objective for biomarkers, implement the legal entity name change, and make small corrections and clarifications.
14 June 2012	The overall reason for the amendment was to add a data cutoff for an interim analysis, to add survival follow-up for those who discontinued treatment, to remove an exclusion criterion for those on intervening treatment for Castleman's disease, and to adapt the Time and Events schedule for the 6-week dosing interval.
17 November 2012	The overall reason for the amendment was to add additional safety evaluations for those subjects entering the study who are naïve to treatment with siltuximab.
04 April 2014	The overall reason for the amendment was to extend the duration of this study to fulfill postmarketing commitments to report safety, efficacy, and survival during long-term treatment with siltuximab, and to stop collecting data that are not required for the final study report.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported