



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 CNT0328MCD2002 included subjects who were previously enrolled in study C0328T03 (NCT00412321) or CNT0328MCD2001 (NCT01024036) (either placebo or siltuximab treatment arm). A total of 60 subjects from previous MCD studies C0328T03 and CNT0328MCD2001 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 CNT0328MCD2001. | |
| 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-naïve Subjects who Experienced Disease Control

| | |
|---|---|
| End point title | Percentage of Siltuximab-naïve 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-naïve i.e., received placebo in study CNT0328MCD2001 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 occurrences (all) | 5 / 60 (8.33%) 6 | | |
| Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) Skin Abrasion subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 5 3 / 60 (5.00%) 3 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Neuropathy Peripheral subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Peripheral Sensory Neuropathy subjects affected / exposed occurrences (all) | 5 / 60 (8.33%) 7 7 / 60 (11.67%) 8 4 / 60 (6.67%) 5 3 / 60 (5.00%) 4 5 / 60 (8.33%) 9 | | |
| Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 5 4 / 60 (6.67%) 36 | | |
| Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all) | 5 / 60 (8.33%) 6 | | |

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

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

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