



Clinical trial results:

A Phase 2, Randomized, Double-blind, Placebo-controlled, Multicenter Study of Siltuximab (Anti IL 6 Monoclonal Antibody) in Subjects with High-risk Smoldering Multiple Myeloma

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2011-001735-22 |
| Trial protocol | BE GB SE FR GR ES DE |
| Global end of trial date | 10 October 2016 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 02 September 2020 |
| First version publication date | 02 September 2020 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | CNT0328SMM2001 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01484275 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Janssen Research & Development, LLC |
| Sponsor organisation address | 1125 Bear Tavern Road, Titusville, United States, NJ 08560 |
| 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 | 10 October 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 October 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate that siltuximab delays the progression of high-risk smoldering multiple myeloma (SMM) as measured by the 1 year Progression-Free Survival (PFS) rate.

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 evaluations included routine clinical laboratory tests (hematology, chemistry, lipid panel, and pregnancy), vital signs, physical examination, weight, infusion related reactions, measurement of antibodies to siltuximab, chest X-ray, and electrocardiogram (ECG) assessment.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 01 March 2012 |
| 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 | Australia: 8 |
| Country: Number of subjects enrolled | Belgium: 2 |
| Country: Number of subjects enrolled | Germany: 19 |
| Country: Number of subjects enrolled | Spain: 15 |
| Country: Number of subjects enrolled | France: 6 |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Country: Number of subjects enrolled | Israel: 10 |
| Country: Number of subjects enrolled | Korea, Republic of: 5 |
| Country: Number of subjects enrolled | United States: 14 |
| Worldwide total number of subjects | 85 |
| EEA total number of subjects | 48 |

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) | 51 |
| From 65 to 84 years | 34 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total of 85 subjects were enrolled in this study (Intent to treat population), 43 subjects were randomized to receive siltuximab and 42 subjects were randomized to receive placebo.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| 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 | Placebo |

Arm description:

Subjects received placebo as a 1-hour IV infusion every 4 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or the end of the study (up to 4 years after randomization of the last subject).

| | |
|--|-----------------|
| 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 4 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or the end of the study (up to 4 years after randomization of the last subject).

| | |
|------------------|------------|
| Arm title | Siltuximab |
|------------------|------------|

Arm description:

Subjects received 15 milligram per kilogram (mg/kg) of siltuximab as a 1-hour intravenous (IV) infusion every 4 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or the end of the study (up to 4 years after randomization of the last subject).

| | |
|--|-----------------|
| 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 15 mg/kg of siltuximab as a 1-hour IV infusion every 4 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or the end of the study (up to 4 years after randomization of the last subject).

| Number of subjects in period 1 | Placebo | Siltuximab |
|---------------------------------------|---------|------------|
| Started | 42 | 43 |
| Completed | 0 | 0 |
| Not completed | 42 | 43 |
| Consent withdrawn by subject | 5 | 1 |
| Death | 4 | 3 |
| Study terminated by sponsor | 32 | 28 |
| Unspecified | - | 10 |
| Lost to follow-up | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|---|------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received placebo as a 1-hour IV infusion every 4 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or the end of the study (up to 4 years after randomization of the last subject). | |
| Reporting group title | Siltuximab |
| Reporting group description: | |
| Subjects received 15 milligram per kilogram (mg/kg) of siltuximab as a 1-hour intravenous (IV) infusion every 4 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or the end of the study (up to 4 years after randomization of the last subject). | |

| Reporting group values | Placebo | Siltuximab | Total |
|---|---------|------------|-------|
| Number of subjects | 42 | 43 | 85 |
| Title for AgeCategorical Units: subjects | | | |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 26 | 25 | 51 |
| From 65 to 84 years | 16 | 18 | 34 |
| 85 years and over | 0 | 0 | 0 |
| Title for AgeContinuous Units: years | | | |
| arithmetic mean | 59.5 | 63.2 | |
| standard deviation | ± 12.03 | ± 10.95 | - |
| Title for Gender Units: subjects | | | |
| Female | 20 | 17 | 37 |
| Male | 22 | 26 | 48 |

End points

End points reporting groups

| | |
|---|------------|
| Reporting group title | Placebo |
| Reporting group description: Subjects received placebo as a 1-hour IV infusion every 4 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or the end of the study (up to 4 years after randomization of the last subject). | |
| Reporting group title | Siltuximab |
| Reporting group description: Subjects received 15 milligram per kilogram (mg/kg) of siltuximab as a 1-hour intravenous (IV) infusion every 4 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or the end of the study (up to 4 years after randomization of the last subject). | |

Primary: One-Year Progression-Free Survival (PFS) Rate

| | |
|---|--|
| End point title | One-Year Progression-Free Survival (PFS) Rate ^[1] |
| End point description: One-year PFS rate is defined as percentage (%) of subjects surviving 1 year after randomization without progression to multiple myeloma or death estimated by Kaplan-Meier method and based on International Myeloma Working Group (IMWG) calcium, renal, anemia, and bone lesions (CRAB) criteria. Progressive disease (PD) is defined as presence of an M-component in serum plus clonal plasma cells in bone marrow plus 1 or more of following: Calcium elevation (greater than [$>$] 11.5 milligram per deciliter [mg/dL] [$>$ 2.88 millimoles per liter {mmol/L}]); Renal insufficiency (creatinine $>$ 2 mg/dL [177 micromoles per liter or more]; Anemia (hemoglobin less than [$<$] 10 gram per deciliter [g/dL] or 2 g/dL lower than lower limit of normal [LLN] [hemoglobin $<$ 6.5 mmol/L or 1.25 mmol/L lower than LLN]); Bone disease (lytic lesions or osteopenia). ITT population included subjects who were randomly assigned to siltuximab or placebo treatment group based on an integrated voice response system (IVRS). | |
| End point type | Primary |
| End point timeframe: Up to 1 Year | |
| 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 | Placebo | Siltuximab | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 43 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 74.4 (57.3 to 85.5) | 84.5 (68.6 to 92.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progressive Disease Indicator Rate (PDIR) at 6 Months

| | |
|-----------------|---|
| End point title | Progressive Disease Indicator Rate (PDIR) at 6 Months |
|-----------------|---|

End point description:

PDIR is defined as percentage of subjects who meet any of following criteria occurring within 6 months of start of treatment. a) CRAB criteria: true progression events, b) Serum M-protein: increase by 25 % compared with baseline at 2 consecutive assessments, c) Magnetic resonance imaging: unequivocal increase in focal bone lesions, d) Immunoparesis: decrease by 25% compared with baseline of 2 other non-affected immunoglobulin (Ig) (IgG, IgM, IgA) at 2 consecutive assessments, e) Hemoglobin: decrease of 1.5 g/dL (with at least 1 read below LLN) at 2 consecutive assessments, with no other identifiable cause. Response evaluable population included subjects who had a diagnosis of high-risk SMM and received at least 1 dose of siltuximab/placebo treatment. In addition, subjects were to have at least 1 post-baseline disease assessment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At 6 Months

| End point values | Placebo | Siltuximab | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 43 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 42.9 (27.7 to 59.0) | 30.2 (17.2 to 46.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

| | |
|-----------------|---------------------------|
| End point title | Progression-Free Survival |
|-----------------|---------------------------|

End point description:

PFS is defined as the time between randomization and initial documented PD according to the CRAB - International Myeloma Working Group (IMWG) criteria or date of death, whichever occurs first. PD is defined as presence of an M-component in serum plus clonal plasma cells in the bone marrow plus 1 or more of the following: Calcium elevation (> 11.5 mg/dL [> 2.88 mmol/L]); Renal insufficiency (creatinine > 2 mg/dL [177 [micro mol/L or more])); Anemia (<10 g/dL or 2 g/dL lower than LLN) [hemoglobin < 6.5 mmol/L or 1.25 mmol/L lower than LLN]); Bone disease (lytic lesions or osteopenia). Intent-to-treat (ITT) population included subjects who were randomly assigned to siltuximab or placebo treatment group based on an IVRS. Here, '99999' signifies that median and upper limit of confidence interval (CI) was not estimable due to less number of events.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 4.7 Years

| End point values | Placebo | Siltuximab | | |
|----------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 43 | | |
| Units: Day | | | | |
| median (confidence interval 95%) | 715.0 (490 to 1232) | 99999 (703 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Serum M-protein Response

| | |
|-----------------|--|
| End point title | Percentage of Subjects with Serum M-protein Response |
|-----------------|--|

End point description:

Serum M-protein response is defined as a decrease of greater than or equal to (\geq) 50% in serum M-protein compared with baseline at 2 consecutive assessments. ITT population included subjects who were randomly assigned to siltuximab or placebo treatment group based on an IVRS.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 4.7 Years

| End point values | Placebo | Siltuximab | | |
|----------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 43 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 0.0 (0.0 to 8.4) | 2.3 (0.1 to 12.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to worsening in European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) Scale Score

| | |
|-----------------|--|
| End point title | Time to worsening in European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) Scale Score |
|-----------------|--|

End point description:

Time to worsening in EORTC-QLQ-C30: Time between randomization and first documentation of a worsening in EORTC-QLQ-C-30, it refers to 10 points decrease from baseline, includes 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, social), 3 symptom scales (fatigue, pain, vomiting), global health, quality of life scale, number of single items assessing symptoms (dyspnea, loss of appetite, insomnia, constipation, diarrhoea). Instrument contains 28 items using Likert scale with 4 response: Not at All, A Little, Quite a Bit, Very Much (scored 1-4). 2 additional items use response options (1-7): 1=Very Poor to 7=Excellent. All scale/ item scores range 0-100. Higher score=higher (better) level of functioning/ higher (worse) level of symptoms. ITT population: subjects assigned to siltuximab/placebo group based on IVRS who had 10 points decrease from baseline in physical function scale.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 4.7 Years

| End point values | Placebo | Siltuximab | | |
|-------------------------------|------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 22 | | |
| Units: Days | | | | |
| median (full range (min-max)) | 118.00 (56.0 to 565.0) | 125.50 (56.0 to 1021.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Worsening in the Brief Pain Inventory (BPI) Worst Item Scores

| | |
|-----------------|---|
| End point title | Time to Worsening in the Brief Pain Inventory (BPI) Worst Item Scores |
|-----------------|---|

End point description:

Time to worsening in BPI worst item is defined as time between randomization and first documentation of a worsening in BPI worst item. It has 2 domains reflecting pain severity and pain interference with domains of functioning and well-being. The selected item refers to "worst" pain patient has experienced over the past 24 hours. This item has been found to be most responsive to interference with key domains of functioning and well-being and may be used as a single item. Responses are provided on an 11-point numeric rating scale ranging from 0 "no pain" to 10 "pain as bad as you can imagine". Responses are described as mild (1 to 4), moderate (5 to 6) and severe (7 to 10). Worsening in BPI worst item is defined as 2 points increase from baseline. ITT population included subjects who were randomly assigned to siltuximab or placebo treatment group based on an IVRS. Here, '99999' signifies that upper limit of CI was not estimable due to an insufficient number of events.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 4.7 Years

| End point values | Placebo | Siltuximab | | |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 43 | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 453.0 (277 to 99999) | 652.0 (226 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Symptomatic Multiple Myeloma with Adverse

Prognostic Features

| | |
|-----------------|---|
| End point title | Number of Subjects with Symptomatic Multiple Myeloma with Adverse Prognostic Features |
|-----------------|---|

End point description:

Number of subjects who progressed to symptomatic multiple myeloma with stage III of International Staging System (ISS) or abnormal cytogenetic findings were assessed. The ISS system consists of stage I: beta2-microglobulin < 3.5 milligram per liter (mg/L) and albumin ≥ 3.5 gram (g)/100 ml; stage II: neither stage I nor stage III and stage III: beta2-microglobulin ≥ 5.5 mg/L.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 4.7 Years

| End point values | Placebo | Siltuximab | | |
|-----------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | | |
| Units: Subjects | | | | |

Notes:

[2] - Data was not collected and analyzed for this endpoint as per the change in planned analysis.

[3] - Data was not collected and analyzed for this endpoint as per the change in planned analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Best Response to First Subsequent Multiple Myeloma Treatment

| | |
|-----------------|--|
| End point title | Number of Subjects with Best Response to First Subsequent Multiple Myeloma Treatment |
|-----------------|--|

End point description:

Best response to first subsequent anti-myeloma therapy was assessed by physician report at 6-month intervals and classified as: complete response (CR) (negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas and < 5% plasma cells (PCs) in bone marrow); stringent CR (CR + a normal FLC ratio, absence of clonal cells in bone marrow); near CR (< 5% PCs in a bone marrow aspirate, no increase in lytic bone lesions); very good partial response (VGPR) (serum and urine component detectable by immunofixation but not on electrophoresis, or ≥ 90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 hour); partial response (PR): ≥ 50 reduction of serum M-protein, reduction in 24-hour urinary M-protein by ≥90 % or to < 200 mg/24 hours); minimal response (≥25% but ≤ 49% reduction of serum M-protein and reduction in urine M-protein by 50%-89%); stable disease (not meeting criteria for CR, VGPR, PR, or PD); PD; not evaluable and unknown.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 4.7 Years

| End point values | Placebo | Siltuximab | | |
|-----------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[4] | 0 ^[5] | | |
| Units: Subjects | | | | |

Notes:

[4] - Data was not collected and analyzed for this endpoint as per the change in planned analysis.

[5] - Data was not collected and analyzed for this endpoint as per the change in planned analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS is defined as the time between randomization and death due to any cause. ITT population included subjects who were randomly assigned to siltuximab or placebo treatment group based on an IVRS. Here, '99999' signifies that median and confidence interval was not estimable due to less number of events.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 4.7 Years

| End point values | Placebo | Siltuximab | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 43 | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 4.7 Years

Adverse event reporting additional description:

Safety analysis set included subjects who have received at least 1 administration of any study agent (siltuximab or placebo).

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received placebo as a 1-hour IV infusion every 4 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or the end of the study (up to 4 years after randomization of the last subject).

| | |
|-----------------------|------------|
| Reporting group title | Siltuximab |
|-----------------------|------------|

Reporting group description:

Subjects received 15 milligram per kilogram (mg/kg) of siltuximab as a 1-hour intravenous (IV) infusion every 4 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or the end of the study (up to 4 years after randomization of the last subject).

| Serious adverse events | Placebo | Siltuximab | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 13 / 42 (30.95%) | 13 / 43 (30.23%) | |
| number of deaths (all causes) | 4 | 3 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon Cancer | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Ischaemia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Poor Venous Access | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal Septum Deviation | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Back Injury | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint Dislocation | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower Limb Fracture | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib Fracture | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal Fracture | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute Coronary Syndrome | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac Arrest | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nervous system disorders | | | |
| Facial Paresis | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient Ischaemic Attack | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Eustachian Tube Disorder | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastric Disorder | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis Acute | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute Kidney Injury | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oliguria | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal Impairment | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back Pain | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 43 (4.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Diverticulitis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower Respiratory Tract Infection | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mastoiditis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otitis Media | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 43 (4.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumonia Streptococcal | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 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 | Siltuximab | |
|---|-------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 42 / 42 (100.00%) | 41 / 43 (95.35%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 1 / 43 (2.33%) | |
| occurrences (all) | 4 | 1 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 8 / 43 (18.60%) | |
| occurrences (all) | 7 | 10 | |
| Chest Pain | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 5 / 42 (11.90%) | 1 / 43 (2.33%) | |
| occurrences (all) | 7 | 1 | |
| Fatigue | | | |
| subjects affected / exposed | 14 / 42 (33.33%) | 6 / 43 (13.95%) | |
| occurrences (all) | 23 | 9 | |
| Influenza Like Illness | | | |
| subjects affected / exposed | 5 / 42 (11.90%) | 1 / 43 (2.33%) | |
| occurrences (all) | 6 | 1 | |
| Oedema Peripheral | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 43 (6.98%) | |
| occurrences (all) | 4 | 3 | |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 42 (14.29%) | 3 / 43 (6.98%) | |
| occurrences (all) | 8 | 3 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 8 / 42 (19.05%) | 8 / 43 (18.60%) | |
| occurrences (all) | 17 | 8 | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 43 (6.98%) | |
| occurrences (all) | 6 | 3 | |
| Epistaxis | | | |
| subjects affected / exposed | 5 / 42 (11.90%) | 0 / 43 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Oropharyngeal Pain | | | |
| subjects affected / exposed | 10 / 42 (23.81%) | 2 / 43 (4.65%) | |
| occurrences (all) | 14 | 2 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 0 / 43 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 0 / 43 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Investigations | | | |

| | | | |
|---|-----------------------|-----------------------|--|
| Alanine Aminotransferase Increased subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 4 / 43 (9.30%) 7 | |
| Aspartate Aminotransferase Increased subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 3 / 43 (6.98%) 3 | |
| Cardiac disorders Palpitations subjects affected / exposed occurrences (all) | 4 / 42 (9.52%) 4 | 1 / 43 (2.33%) 1 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 6 / 42 (14.29%) 7 | 3 / 43 (6.98%) 3 | |
| Headache subjects affected / exposed occurrences (all) | 9 / 42 (21.43%) 14 | 6 / 43 (13.95%) 12 | |
| Sciatica subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 2 | 4 / 43 (9.30%) 4 | |
| Syncope subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 3 / 43 (6.98%) 3 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 6 / 42 (14.29%) 6 | 6 / 43 (13.95%) 10 | |
| Neutropenia subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 2 | 8 / 43 (18.60%) 42 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 5 / 43 (11.63%) 5 | |
| Gastrointestinal disorders Abdominal Distension | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 4 / 42 (9.52%) | 0 / 43 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Abdominal Pain | | | |
| subjects affected / exposed | 6 / 42 (14.29%) | 3 / 43 (6.98%) | |
| occurrences (all) | 9 | 4 | |
| Abdominal Pain Lower | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 1 / 43 (2.33%) | |
| occurrences (all) | 3 | 1 | |
| Abdominal Pain Upper | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 2 / 43 (4.65%) | |
| occurrences (all) | 4 | 3 | |
| Constipation | | | |
| subjects affected / exposed | 7 / 42 (16.67%) | 5 / 43 (11.63%) | |
| occurrences (all) | 12 | 7 | |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 42 (16.67%) | 6 / 43 (13.95%) | |
| occurrences (all) | 7 | 7 | |
| Nausea | | | |
| subjects affected / exposed | 10 / 42 (23.81%) | 9 / 43 (20.93%) | |
| occurrences (all) | 17 | 15 | |
| Stomatitis | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 2 / 43 (4.65%) | |
| occurrences (all) | 3 | 4 | |
| Skin and subcutaneous tissue disorders | | | |
| Night Sweats | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 43 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Rash | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 6 / 43 (13.95%) | |
| occurrences (all) | 0 | 6 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 11 / 42 (26.19%) | 5 / 43 (11.63%) | |
| occurrences (all) | 15 | 7 | |
| Back Pain | | | |

| | | | |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 12 / 42 (28.57%) | 10 / 43 (23.26%) | |
| occurrences (all) | 18 | 10 | |
| Muscle Spasms | | | |
| subjects affected / exposed | 5 / 42 (11.90%) | 0 / 43 (0.00%) | |
| occurrences (all) | 11 | 0 | |
| Musculoskeletal Chest Pain | | | |
| subjects affected / exposed | 9 / 42 (21.43%) | 5 / 43 (11.63%) | |
| occurrences (all) | 9 | 6 | |
| Myalgia | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 2 / 43 (4.65%) | |
| occurrences (all) | 4 | 2 | |
| Pain in Extremity | | | |
| subjects affected / exposed | 8 / 42 (19.05%) | 5 / 43 (11.63%) | |
| occurrences (all) | 13 | 7 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 43 (6.98%) | |
| occurrences (all) | 6 | 4 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 3 / 43 (6.98%) | |
| occurrences (all) | 1 | 3 | |
| Herpes Zoster | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 1 / 43 (2.33%) | |
| occurrences (all) | 4 | 2 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 15 / 42 (35.71%) | 9 / 43 (20.93%) | |
| occurrences (all) | 31 | 20 | |
| Oral Herpes | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 0 / 43 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 3 / 43 (6.98%) | |
| occurrences (all) | 1 | 3 | |
| Rhinitis | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 1 / 43 (2.33%) | |
| occurrences (all) | 7 | 1 | |

| | | | |
|------------------------------------|------------------|-----------------|--|
| Sinusitis | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 43 (6.98%) | |
| occurrences (all) | 5 | 3 | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 10 / 42 (23.81%) | 5 / 43 (11.63%) | |
| occurrences (all) | 17 | 11 | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 3 / 43 (6.98%) | |
| occurrences (all) | 7 | 3 | |
| Metabolism and nutrition disorders | | | |
| Decreased Appetite | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 3 / 43 (6.98%) | |
| occurrences (all) | 0 | 3 | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 4 / 43 (9.30%) | |
| occurrences (all) | 0 | 6 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 17 February 2012 | The overall reason for the amendment was to add a patient-reported outcome questionnaire (Non-Chemotherapy Anemia Symptom Scale [NCA-SS]), and to provide clarification on sections of the protocol, as specified below. In addition, an update to the company sponsorship information was required. |
| 25 October 2012 | The overall reason for the amendment was to broaden the high-risk SMM patient population by revising the inclusion criterion and the related stratification risk factor definition. |
| 15 May 2013 | The overall reason for the amendment was the duration of the study was substantially longer than planned because of slow recruitment. In order to evaluate if the study can achieve its objectives and to prevent subjects from being exposed to a potentially ineffective treatment, a formal futility analysis was incorporated. |
| 13 January 2014 | The overall reason for the amendment was after review of data from the futility analysis added per Amendment INT 3, the Steering Committee has recommended to continue the study and implement an additional interim futility analysis with progression event rate as an endpoint. |
| 13 February 2015 | The overall reason for the amendment was the accrual into the study was almost stopped due to a combination of changed clinical guidelines with respect to treatment of high-risk smoldering multiple myeloma (SMM) patients as well as the increased number of clinical studies within the indication. Given the longer recruitment time and thus total longer cumulative follow up time, timing of primary analysis has been moved forward, thereby making the interim analysis at 6 months redundant. |
| 09 May 2016 | The overall reason for the amendment was to ensure that ongoing subjects benefitted from siltuximab treatment can continue to receive siltuximab in an Open-Label Extension of the study. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Siltuximab demonstrated positive trending toward 1-year PFS only in high risk SMM-group. Sponsor and Steering Committee decided not to further pursue clinical development of siltuximab for SMM and terminated study, and was considered as completed.

Notes: