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	CNTO328SMM2001

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