Clinical trial results:
A Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of Amatuximab in Combination with Pemetrexed and Cisplatin in Subjects with Unresectable Malignant Pleural Mesothelioma

Summary

EudraCT number	2014-004489-85
Trial protocol	DE IT
Global end of trial date	30 November 2018

Results information

Result version number	v1 (current)
This version publication date	03 April 2020
First version publication date	03 April 2020

Trial information

Trial identification

Sponsor protocol code	MORAb-009-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02357147
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Morphotek (a subsidiary of Eisai Inc.)
Sponsor organisation address	155 Tice Boulevard, Woodcliff Lake, New Jersey, United States, 07677
Public contact	EISAI Medical Information, Eisai Ltd., +1 888-274-2378, esi_oncmedinfo@eisai.com
Scientific contact	EISAI Medical Information, Eisai Ltd., +1 888-274-2378, esi_oncmedinfo@eisai.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	30 November 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 November 2018
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 provide ongoing amatuximab treatment access consistent with the original MORAb-009-201 treatment schedule to those subjects randomized to the amatuximab arm who, at the discretion of their investigator, may obtain ongoing clinical benefit.

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: - Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008) - International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use -Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312 - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states. -Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan’s GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Italy: 43
Worldwide total number of subjects	106
EEA total number of subjects	96

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)	33
From 65 to 84 years	72
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 36 investigative sites in the United States, France, Germany, Italy, the United Kingdom, and Australia from 03 November 2015 to 30 November 2018.

Pre-assignment

Screening details:

A total of 124 subjects were enrolled (signed informed consent form), of which, 16 were screen failures, 108 were randomized, and 106 were treated. Deaths that were primary cause of treatment discontinuation are reported in subject flow excluding those that occurred after treatment discontinuation.

Period 1

Period 1 title	Combination Treatment Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Amatuximab + Pemetrexed + Cisplatin

Arm description:

During combination treatment phase, subjects received amatuximab 5 milligram per kilogram (mg/kg), infusion, intravenously, once weekly in 21-day cycles and pemetrexed 500 milligram per square meter (mg/m^2) and cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles. Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and continued to receive amatuximab 5 mg/kg, infusion, intravenously, once weekly until disease progression.

Arm type	Experimental
Investigational medicinal product name	Amatuximab
Investigational medicinal product code	MORAb-009
Other name	MORAb-009
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During Combination Treatment Phase, subjects received amatuximab 5 mg/kg, infusion, intravenously, once weekly in 21-day cycles. Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and continued to receive amatuximab 5 mg/kg, infusion, intravenously, once weekly until disease progression.

Investigational medicinal product name	Premetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During Combination Treatment Phase, subjects received pemetrexed 500 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During Combination Treatment Phase, subjects received cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles.

Arm title	Placebo + Pemetrexed + Cisplatin

Arm description:

During combination treatment phase, subjects received placebo matched to amatuximab infusion, intravenously, once weekly in 21-day cycles and pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles. Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and received placebo matched to amatuximab infusion, intravenously, once weekly until disease progression.

Arm type	Placebo and experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During Combination Treatment Phase, subjects received placebo matched to amatuximab infusion, intravenously, once weekly in 21-day cycles. Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and continued to receive placebo matched to amatuximab infusion, infusion, intravenously, once weekly until disease progression.

Investigational medicinal product name	Premetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During Combination Treatment Phase, subjects received pemetrexed 500 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During Combination Treatment Phase, subjects received cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles.

Number of subjects in period 1	Amatuximab + Pemetrexed + Cisplatin	Placebo + Pemetrexed + Cisplatin
Started	52	54
Completed	26	29
Not completed	26	25
Progressive Disease (Radiographic test)	3	3
Consent withdrawn by subject	4	2
Adverse event, non-fatal	12	4

Death	1	1
Other	1	-
Investigator Discretion	1	1
Test Article Held for Greater than 21Day	4	1
Sponsor Decision	-	12
Progressive Disease(Clinical assessment)	-	1

Period 2

Period 2 title	Maintenance Treatment Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Amatuximab + Pemetrexed + Cisplatin

Arm description:

During combination treatment phase, subjects received amatuximab 5 mg/kg, infusion, intravenously, once weekly in 21-day cycles and pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles. Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and continued to receive amatuximab 5 mg/kg, infusion, intravenously, once weekly until disease progression.

Arm type	Experimental
Investigational medicinal product name	Amatuximab
Investigational medicinal product code	MORAb-009
Other name	MORAb-009
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During Combination Treatment Phase, subjects received amatuximab 5 mg/kg, infusion, intravenously, once weekly in 21-day cycles. Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and continued to receive amatuximab 5 mg/kg, infusion, intravenously, once weekly until disease progression.

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During Combination Treatment Phase, subjects received pemetrexed 500 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During Combination Treatment Phase, subjects received cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles.

Arm title	Placebo + Pemetrexed + Cisplatin

Arm description:

During combination treatment phase, subjects received placebo matched to amatuximab infusion, intravenously, once weekly in 21-day cycles and pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles. Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and received placebo matched to amatuximab infusion, intravenously, once weekly until disease progression.

Arm type	Placebo and experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During Combination Treatment Phase, subjects received placebo matched to amatuximab infusion, infusion, intravenously, once weekly in 21-day cycles. Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and continued to receive placebo matched to amatuximab infusion, infusion, intravenously, once weekly until disease progression.

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During Combination Treatment Phase, subjects received pemetrexed 500 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During Combination Treatment Phase, subjects received cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles.

Number of subjects in period 2	Amatuximab + Pemetrexed + Cisplatin	Placebo + Pemetrexed + Cisplatin
Started	26	29
Treated	25	29
Completed	0	0
Not completed	26	29
Progressive Disease (Radiographic test)	15	10
Consent withdrawn by subject	-	1

Adverse event, non-fatal	-	3
Not Treated	1	-
Test Article Held for Greater than 21Day	10	-
Sponsor Decision	-	15

Baseline characteristics

Reporting groups	
Reporting group title	Amatuximab + Pemetrexed + Cisplatin

Reporting group description:

During combination treatment phase, subjects received amatuximab 5 milligram per kilogram (mg/kg), infusion, intravenously, once weekly in 21-day cycles and pemetrexed 500 milligram per square meter (mg/m^2) and cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles. Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and continued to receive amatuximab 5 mg/kg, infusion, intravenously, once weekly until disease progression.

Reporting group title	Placebo + Pemetrexed + Cisplatin

Reporting group description:

During combination treatment phase, subjects received placebo matched to amatuximab infusion, intravenously, once weekly in 21-day cycles and pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles. Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and received placebo matched to amatuximab infusion, intravenously, once weekly until disease progression.

Reporting group values	Amatuximab + Pemetrexed + Cisplatin	Placebo + Pemetrexed + Cisplatin	Total
Number of subjects	52	54	106
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	18	33
From 65-84 years	37	35	72
85 years and over	0	1	1
Age continuous Units: years			
arithmetic mean	67.90	66.90	
standard deviation	± 6.08	± 7.96	-
Gender categorical Units: Subjects			
Female	15	14	29
Male	37	40	77
Ethnicity characteristics Units: Subjects			
Hispanic or Latino	1	7	8
Not Hispanic or Latino	42	37	79
Unknown or Not Reported	9	10	19
Race characteristics Units: Subjects			
Asian	1	0	1
Black or African American	0	1	1

White	45	46	91
Unknown or Not Reported	6	7	13

End points reporting groups

Reporting group title	Amatuximab + Pemetrexed + Cisplatin

Reporting group description:

During combination treatment phase, subjects received amatuximab 5 milligram per kilogram (mg/kg), infusion, intravenously, once weekly in 21-day cycles and pemetrexed 500 milligram per square meter (mg/m^2) and cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles. Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and continued to receive amatuximab 5 mg/kg, infusion, intravenously, once weekly until disease progression.

Reporting group title	Placebo + Pemetrexed + Cisplatin

Reporting group description:

During combination treatment phase, subjects received placebo matched to amatuximab infusion, intravenously, once weekly in 21-day cycles and pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles. Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and received placebo matched to amatuximab infusion, intravenously, once weekly until disease progression.

Reporting group title	Amatuximab + Pemetrexed + Cisplatin

Reporting group description:

During combination treatment phase, subjects received amatuximab 5 mg/kg, infusion, intravenously, once weekly in 21-day cycles and pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles. Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and continued to receive amatuximab 5 mg/kg, infusion, intravenously, once weekly until disease progression.

Reporting group title	Placebo + Pemetrexed + Cisplatin

Reporting group description:

During combination treatment phase, subjects received placebo matched to amatuximab infusion, intravenously, once weekly in 21-day cycles and pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles. Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and received placebo matched to amatuximab infusion, intravenously, once weekly until disease progression.

Subject analysis set title	Combination Treatment Phase:Amatuximab + Pemetrexed +Cisplatin
Subject analysis set type	Safety analysis

Subject analysis set description:

During combination treatment phase, subjects received amatuximab 5 mg/kg, infusion, intravenously, once weekly in 21-day cycles and pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles.

Subject analysis set title	Combination Treatment Phase: Placebo + Pemetrexed + Cisplatin
Subject analysis set type	Safety analysis

Subject analysis set description:

During combination treatment phase, subjects received placebo matched to amatuximab infusion, intravenously, once weekly in 21-day cycles and pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles.

Subject analysis set title	Maintenance Treatment Phase: Amatuximab
Subject analysis set type	Safety analysis

Subject analysis set description:

Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and continued to receive amatuximab 5 mg/kg, infusion, intravenously, once weekly until disease progression.

Subject analysis set title	Maintenance Treatment Phase: Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and received placebo matched to amatuximab infusion, intravenously, once weekly until disease progression.

Primary: Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)[1]

End point description:

AEs includes both non-SAEs and SAEs and the same subject can have both SAEs and as well non-SAEs. The safety analysis set was defined as all randomized subjects who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline up to 3 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: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Combination Treatment Phase:Amatuximab + Pemetrexed +Cisplatin	Combination Treatment Phase: Placebo + Pemetrexed + Cisplatin	Maintenance Treatment Phase: Amatuximab	Maintenance Treatment Phase: Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	52	54	25	29
Units: subjects				
AEs	50	52	19	21
SAEs	15	11	1	4

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug up to 30 days after the last dose of study drug or until date of death (approximately up to 3 years)

Adverse event reporting additional description:

Deaths that happened anytime during the study (including those during the treatment and after treatment discontinuation) are reported in this section.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Combination Treatment Phase:Amatuximab + Pemetrexed +Cisplatin

Reporting group description:

During combination treatment phase, subjects received amatuximab 5 mg/kg, infusion, intravenously, once weekly in 21-day cycles and pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles.

Reporting group title	Combination Treatment Phase: Placebo + Pemetrexed + Cisplatin

Reporting group description:

During combination treatment phase, subjects received placebo matched to amatuximab infusion, intravenously, once weekly in 21-day cycles and pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, infusion, intravenously, on Day 1 of each 21-day cycle for 6 cycles.

Reporting group title	Maintenance Treatment Phase: Amatuximab

Reporting group description:

Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and continued to receive amatuximab 5 mg/kg, infusion, intravenously, once weekly until disease progression.

Reporting group title	Maintenance Treatment Phase: Placebo

Reporting group description:

Following completion of the Combination Treatment Phase, subjects who had not progressed entered the Maintenance Phase and received placebo matched to amatuximab infusion, intravenously, once weekly until disease progression.

Serious adverse events	Combination Treatment Phase:Amatuximab + Pemetrexed +Cisplatin	Combination Treatment Phase: Placebo + Pemetrexed + Cisplatin	Maintenance Treatment Phase: Amatuximab
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 52 (28.85%)	11 / 54 (20.37%)	1 / 25 (4.00%)
number of deaths (all causes)	6	3	2
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			

subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 52 (1.92%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 52 (1.92%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 52 (0.00%)	2 / 54 (3.70%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Organic brain syndrome			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 52 (3.85%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	0 / 52 (0.00%)	2 / 54 (3.70%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Amaurosis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 52 (3.85%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nausea			
subjects affected / exposed	3 / 52 (5.77%)	2 / 54 (3.70%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 52 (0.00%)	2 / 54 (3.70%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 52 (1.92%)	2 / 54 (3.70%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 52 (1.92%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 52 (1.92%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	2 / 52 (3.85%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			

subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 52 (3.85%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Maintenance Treatment Phase: Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 29 (13.79%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chills				
subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				

subjects affected / exposed	0 / 29 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Organic brain syndrome			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	0 / 29 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Amaurosis			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Nausea				
subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain				
subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cellulitis				
subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				

subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mucosal infection				
subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypokalaemia				
subjects affected / exposed	0 / 29 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Combination Treatment Phase:Amatuximab + Pemetrexed +Cisplatin	Combination Treatment Phase: Placebo + Pemetrexed + Cisplatin	Maintenance Treatment Phase: Amatuximab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 52 (96.15%)	51 / 54 (94.44%)	19 / 25 (76.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 52 (1.92%)	3 / 54 (5.56%)	0 / 25 (0.00%)
occurrences (all)	1	4	0
Vascular disorders			

Hypertension			
subjects affected / exposed	3 / 52 (5.77%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences (all)	6	0	0
Hypotension			
subjects affected / exposed	4 / 52 (7.69%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences (all)	4	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 52 (21.15%)	18 / 54 (33.33%)	1 / 25 (4.00%)
occurrences (all)	18	48	8
Chills			
subjects affected / exposed	6 / 52 (11.54%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	6	2	0
Fatigue			
subjects affected / exposed	18 / 52 (34.62%)	19 / 54 (35.19%)	3 / 25 (12.00%)
occurrences (all)	27	31	3
Non-cardiac chest pain			
subjects affected / exposed	4 / 52 (7.69%)	3 / 54 (5.56%)	2 / 25 (8.00%)
occurrences (all)	5	3	2
Oedema peripheral			
subjects affected / exposed	3 / 52 (5.77%)	3 / 54 (5.56%)	0 / 25 (0.00%)
occurrences (all)	3	6	0
Pyrexia			
subjects affected / exposed	7 / 52 (13.46%)	3 / 54 (5.56%)	0 / 25 (0.00%)
occurrences (all)	8	5	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 52 (15.38%)	6 / 54 (11.11%)	4 / 25 (16.00%)
occurrences (all)	12	6	7
Dyspnoea			
subjects affected / exposed	9 / 52 (17.31%)	3 / 54 (5.56%)	4 / 25 (16.00%)
occurrences (all)	10	4	7
Hiccups			
subjects affected / exposed	1 / 52 (1.92%)	3 / 54 (5.56%)	0 / 25 (0.00%)
occurrences (all)	1	3	0
Productive cough			

subjects affected / exposed	4 / 52 (7.69%)	3 / 54 (5.56%)	2 / 25 (8.00%)
occurrences (all)	4	3	2
Pulmonary embolism			
subjects affected / exposed	3 / 52 (5.77%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	3	1	0
Epistaxis			
subjects affected / exposed	4 / 52 (7.69%)	2 / 54 (3.70%)	1 / 25 (4.00%)
occurrences (all)	5	2	1
Dyspnoea exertional			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	2 / 25 (8.00%)
occurrences (all)	1	0	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 52 (7.69%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	4	1	0
Insomnia			
subjects affected / exposed	3 / 52 (5.77%)	4 / 54 (7.41%)	0 / 25 (0.00%)
occurrences (all)	3	4	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 52 (0.00%)	3 / 54 (5.56%)	0 / 25 (0.00%)
occurrences (all)	0	3	0
Blood bilirubin increased			
subjects affected / exposed	0 / 52 (0.00%)	3 / 54 (5.56%)	0 / 25 (0.00%)
occurrences (all)	0	3	0
Blood creatinine increased			
subjects affected / exposed	3 / 52 (5.77%)	6 / 54 (11.11%)	0 / 25 (0.00%)
occurrences (all)	5	7	0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	6 / 52 (11.54%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences (all)	9	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0

Nervous system disorders			
Dysgeusia			
subjects affected / exposed	5 / 52 (9.62%)	6 / 54 (11.11%)	0 / 25 (0.00%)
occurrences (all)	5	8	0
Headache			
subjects affected / exposed	6 / 52 (11.54%)	4 / 54 (7.41%)	1 / 25 (4.00%)
occurrences (all)	6	4	1
Paraesthesia			
subjects affected / exposed	7 / 52 (13.46%)	2 / 54 (3.70%)	3 / 25 (12.00%)
occurrences (all)	9	3	4
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 52 (3.85%)	5 / 54 (9.26%)	0 / 25 (0.00%)
occurrences (all)	2	9	0
Tremor			
subjects affected / exposed	2 / 52 (3.85%)	3 / 54 (5.56%)	0 / 25 (0.00%)
occurrences (all)	2	3	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 52 (21.15%)	12 / 54 (22.22%)	3 / 25 (12.00%)
occurrences (all)	29	21	11
Leukopenia			
subjects affected / exposed	3 / 52 (5.77%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	3	1	0
Neutropenia			
subjects affected / exposed	13 / 52 (25.00%)	10 / 54 (18.52%)	2 / 25 (8.00%)
occurrences (all)	35	28	2
Thrombocytopenia			
subjects affected / exposed	5 / 52 (9.62%)	1 / 54 (1.85%)	1 / 25 (4.00%)
occurrences (all)	7	1	1
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	5 / 52 (9.62%)	3 / 54 (5.56%)	0 / 25 (0.00%)
occurrences (all)	6	4	0
Eye disorders			
Dry eye			
subjects affected / exposed	3 / 52 (5.77%)	2 / 54 (3.70%)	0 / 25 (0.00%)
occurrences (all)	3	2	0

Lacrimation increased			
subjects affected / exposed	4 / 52 (7.69%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	5	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 52 (5.77%)	2 / 54 (3.70%)	2 / 25 (8.00%)
occurrences (all)	3	4	2
Abdominal pain upper			
subjects affected / exposed	2 / 52 (3.85%)	5 / 54 (9.26%)	1 / 25 (4.00%)
occurrences (all)	5	5	2
Constipation			
subjects affected / exposed	17 / 52 (32.69%)	22 / 54 (40.74%)	1 / 25 (4.00%)
occurrences (all)	27	32	2
Diarrhoea			
subjects affected / exposed	11 / 52 (21.15%)	10 / 54 (18.52%)	3 / 25 (12.00%)
occurrences (all)	17	13	3
Dyspepsia			
subjects affected / exposed	7 / 52 (13.46%)	9 / 54 (16.67%)	1 / 25 (4.00%)
occurrences (all)	8	10	1
Nausea			
subjects affected / exposed	34 / 52 (65.38%)	39 / 54 (72.22%)	1 / 25 (4.00%)
occurrences (all)	78	83	1
Stomatitis			
subjects affected / exposed	6 / 52 (11.54%)	13 / 54 (24.07%)	0 / 25 (0.00%)
occurrences (all)	7	21	0
Vomiting			
subjects affected / exposed	13 / 52 (25.00%)	18 / 54 (33.33%)	2 / 25 (8.00%)
occurrences (all)	25	34	2
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 52 (1.92%)	3 / 54 (5.56%)	1 / 25 (4.00%)
occurrences (all)	1	3	1
Dry skin			
subjects affected / exposed	2 / 52 (3.85%)	4 / 54 (7.41%)	1 / 25 (4.00%)
occurrences (all)	2	4	1
Hyperhidrosis			

subjects affected / exposed	2 / 52 (3.85%)	1 / 54 (1.85%)	1 / 25 (4.00%)
occurrences (all)	2	1	1
Pruritus			
subjects affected / exposed	3 / 52 (5.77%)	0 / 54 (0.00%)	0 / 25 (0.00%)
occurrences (all)	3	0	0
Rash			
subjects affected / exposed	6 / 52 (11.54%)	7 / 54 (12.96%)	2 / 25 (8.00%)
occurrences (all)	6	10	2
Night sweats			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 52 (3.85%)	5 / 54 (9.26%)	1 / 25 (4.00%)
occurrences (all)	4	6	1
Musculoskeletal chest pain			
subjects affected / exposed	2 / 52 (3.85%)	2 / 54 (3.70%)	2 / 25 (8.00%)
occurrences (all)	2	2	2
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	4 / 52 (7.69%)	4 / 54 (7.41%)	0 / 25 (0.00%)
occurrences (all)	6	7	0
Nasopharyngitis			
subjects affected / exposed	4 / 52 (7.69%)	1 / 54 (1.85%)	3 / 25 (12.00%)
occurrences (all)	4	1	3
Tooth abscess			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Influenza			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 52 (26.92%)	17 / 54 (31.48%)	1 / 25 (4.00%)
occurrences (all)	23	25	1
Dehydration			

subjects affected / exposed	3 / 52 (5.77%)	2 / 54 (3.70%)	0 / 25 (0.00%)
occurrences (all)	3	2	0
Hypokalaemia			
subjects affected / exposed	3 / 52 (5.77%)	3 / 54 (5.56%)	0 / 25 (0.00%)
occurrences (all)	4	3	0
Hypomagnesaemia			
subjects affected / exposed	2 / 52 (3.85%)	3 / 54 (5.56%)	0 / 25 (0.00%)
occurrences (all)	2	3	0
Hyponatraemia			
subjects affected / exposed	1 / 52 (1.92%)	3 / 54 (5.56%)	0 / 25 (0.00%)
occurrences (all)	1	5	0

Non-serious adverse events	Maintenance Treatment Phase: Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 29 (72.41%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 29 (20.69%)		
occurrences (all)	9		
Chills			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Fatigue			

subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Non-cardiac chest pain			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 29 (17.24%)		
occurrences (all)	6		
Dyspnoea			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Hiccups			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Pulmonary embolism			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Dyspnoea exertional			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			

Anxiety subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0		
Insomnia subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0		
Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0		
Blood creatinine increased subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0		
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1		
Headache subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1		
Paraesthesia subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1		
Peripheral sensory neuropathy			

subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	6		
Tremor			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Leukopenia			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Thrombocytopenia			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Lacrimation increased			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Constipation			

subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	4		
Stomatitis			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Night sweats			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Tooth abscess			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Dehydration			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Hypomagnesaemia			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2015	Updated the inclusion and exclusion criteria, Quality of Life measurements was corrected from 6 subcategories to 5, and removed hemoptysis, added clarity on protocol conduct, ensured consistent terminology used throughout document, added clarity on administration of premedications, and other editorial changes.
30 January 2017	Removed all the efficacy endpoints.

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.

The study was terminated due to business decision. No safety concerns involved in decision to terminate this study.

Notes: