Clinical trial results:
A 3-Arm Phase 2 Double-Blind Randomized Study of Carboplatin, Pemetrexed Plus Placebo versus Carboplatin, Pemetrexed plus 1 or 2 Truncated Courses of Demcizumab in Subjects with Non-Squamous Non-Small Cell Lung Cancer

Summary

EudraCT number	2014-003356-30
Trial protocol	ES BE IT DE
Global end of trial date	07 April 2017

Results information

Result version number	v1 (current)
This version publication date	30 November 2017
First version publication date	30 November 2017

Trial information

Trial identification

Sponsor protocol code	M18-007

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	OncoMed Pharmaceuticals, Inc
Sponsor organisation address	800 Chesapeake Drive, Redwood City, United States, CA 94063
Public contact	Senior Vice President Clinical Research Robert Stagg, Pharm. D., OncoMed Pharmaceuticals, Inc., 1 650-995-8200, bob.stagg@oncomed.com
Scientific contact	Senior Vice President Clinical Research Robert Stagg, Pharm. D., OncoMed Pharmaceuticals, Inc., 1 650-995-8200, bob.stagg@oncomed.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	31 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 April 2017
Global end of trial reached?	Yes
Global end of trial date	07 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of Arm 1 to Arm 2 and Arm 1 to Arm 3 in subjects with 1st-line stage IV non-squamous non-small cell lung cancer

Protection of trial subjects:

In the absence of unacceptable toxicities or disease progression per RECIST v1.1, subjects continued to receive study treatment. Regardless of discontinuation of one, two, or all three study drugs, subjects could continue on study with assessments. Once discontinuation criteria for the study were met (disease progression, use of other anticancer therapy, subject or investigator decision or protocol non-compliance), a termination visit occurred ≤14 days later. Subjects who did not meet the criteria to receive the second 4-cycle course of placebo or demcizumab continued to receive maintenance pemetrexed per protocol without demcizumab or placebo.

To reduce gastrointestinal and hematologic toxicity, subjects received oral folic acid of ≥400 µg daily for at least 5 of the 7 days preceding the first dose of pemetrexed and continued daily during the full course of therapy and for 21 days after the last dose of pemetrexed. Subjects also received an intramuscular injection of vitamin B12 1000 µg during the week preceding the first dose of pemetrexed and then every 63 days while being treated with pemetrexed. Unless contraindicated, subjects also received dexamethasone 4 mg orally twice daily on the day before, the day of, and
the day after pemetrexed administration to reduce the risk of developing skin rash.

Background therapy:

Carboplatin and pemetrexed were administered once every 3 weeks for 4 cycles and then pemetrexed only was administered as once every 3 weeks as maintenance therapy.

Evidence for comparator:

Placebo was used as reference therapy. There were no any patients treated with placebo as a single medication. The placebo was used only as a comparator in addition to standard treatment scheme.

Actual start date of recruitment	03 February 2015
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	Spain: 20
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Australia: 33
Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	82
EEA total number of subjects	29

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)	49
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 55 active centers in North America, Western Europe, and Australia. This was a randomized, double-blind, 3-arm (1:1:1) study in subjects with first-line Stage IV non-squamous NSCLC.

Pre-assignment

Screening details:

Subjects aged ≥21 years with cytologically or histologically confirmed Stage IV non-squamous NSCLC were included. Subjects were not included if they had histologically or cytologically documented, advanced, mixed non-small cell and small cell tumors or mixed adenosquamous carcinomas.

Period 1

Period 1 title	Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/placebo arm (Arm 1)

Arm description:

Placebo plus pemetrexed and carboplatin (4 cycles), pemetrexed (4 cycles), placebo plus pemetrexed (4 cycles).

Arm type	Placebo
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:

A necessary amount placebo was withdrawn to obtain the required dose and diluted with 5% dextrose in water, USP, to a total volume of 250 ml.

Placebo was a clear to slightly opalescent, colorless to slightly yellow, liquid formulation of 50 mM histidine, 100 mM sodium chloride, 45 mM sucrose, and 0.01% (v/v) polysorbate-20, pH 6.0. Placebo was administered first, followed by pemetrexed, and then carboplatin immediately afterwards.

Arm title	Demcizumab/placebo arm (Arm 2)

Arm description:

Demcizumab plus pemetrexed and carboplatin (4 cycles), pemetrexed (4 cycles), placebo plus pemetrexed (4 cycles).

Arm type	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:

A necessary amount placebo was withdrawn to obtain the required dose and diluted with 5% dextrose in water, USP, to a total volume of 250 ml.

Placebo was a clear to slightly opalescent, colorless to slightly yellow, liquid formulation of 50 mM histidine, 100 mM sodium chloride, 45 mM sucrose, and 0.01% (v/v) polysorbate-20, pH 6.0. Placebo

was administered first, followed by pemetrexed, and then carboplatin immediately afterwards.

Investigational medicinal product name	Demcizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Demcizumab was supplied at a concentration of 10 mg/mL in a 25-mL single-use glass vial filled to 20 mL to deliver a total of 200 mg per vial. Demcizumab and placebo vials were to be refrigerated at 2°C to 8°C. Demcizumab and placebo were not to be shaken or frozen.

Demcizumab 5 mg/kg or placebo was administered once every 3 weeks for 4 cycles (i.e., the last administration on Day 63). A second course of Demcizumab 5 mg/kg or placebo was administered once every 3 weeks for 63 days starting at Day 168 only if they met the original cardiac-related eligibility criteria (see exclusion criterion 21), they did not develop pulmonary hypertension or heart failure while on study, and blood pressure was controlled to ≤140/90 mm Hg.

Arm title	Demcizumab/demcizumab arm (Arm 3)

Arm description:

Demcizumab plus pemetrexed and carboplatin (4 cycles), pemetrexed (4 cycles), demcizumab plus pemetrexed (4 cycles).

Arm type	Experimental
Investigational medicinal product name	Demcizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Demcizumab was supplied at a concentration of 10 mg/mL in a 25-mL single-use glass vial filled to 20 mL to deliver a total of 200 mg per vial. Demcizumab and placebo vials were to be refrigerated at 2°C to 8°C. Demcizumab and placebo were not to be shaken or frozen.

Demcizumab 5 mg/kg or placebo was administered once every 3 weeks for 4 cycles (i.e., the last administration on Day 63). A second course of Demcizumab 5 mg/kg or placebo was administered once every 3 weeks for 63 days starting at Day 168 only if they met the original cardiac-related eligibility criteria (see exclusion criterion 21), they did not develop pulmonary hypertension or heart failure while on study, and blood pressure was controlled to ≤140/90 mm Hg.

Number of subjects in period 1	Placebo/placebo arm (Arm 1)	Demcizumab/placebo arm (Arm 2)	Demcizumab/demcizumab arm (Arm 3)
Started	25	28	29
Completed	9	11	8
Not completed	16	17	21
Physician decision	-	1	-
Consent withdrawn by subject	-	-	1
death	-	-	1
Adverse event, non-fatal	1	-	1
other	1	1	1
desease progression	14	15	17

Baseline characteristics

Reporting groups	
Reporting group title	Placebo/placebo arm (Arm 1)
Reporting group description:	
Placebo plus pemetrexed and carboplatin (4 cycles), pemetrexed (4 cycles), placebo plus pemetrexed (4 cycles).	
Reporting group title	Demcizumab/placebo arm (Arm 2)
Reporting group description:	
Demcizumab plus pemetrexed and carboplatin (4 cycles), pemetrexed (4 cycles), placebo plus pemetrexed (4 cycles).	
Reporting group title	Demcizumab/demcizumab arm (Arm 3)
Reporting group description:	
Demcizumab plus pemetrexed and carboplatin (4 cycles), pemetrexed (4 cycles), demcizumab plus pemetrexed (4 cycles).	

Reporting group values	Placebo/placebo arm (Arm 1)	Demcizumab/placebo arm (Arm 2)	Demcizumab/demcizumab arm (Arm 3)
Number of subjects	25	28	29
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	60	66	61
full range (min-max)	40 to 77	31 to 76	39 to 76
Gender categorical Units: Subjects			
Female	15	15	12
Male	10	13	17

Reporting group values	Total		
Number of subjects	82		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	42		
Male	40		

Subject analysis sets

Subject analysis set title	Intent-to-treat (ITT) Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Population comprised all subjects who were randomized. Subjects were analyzed as they were randomized.

Subject analysis set title	Per-protocol (PP) Population
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population comprised all subjects who received at least 1 dose of demcizumab or placebo and had at least 1 postbaseline tumor assessment. Subjects were analyzed as they were treated. Efficacy, immunogenicity, and biomarker data was analyzed using the PP population as well as the ITT population.

Reporting group values	Intent-to-treat (ITT) Population	Per-protocol (PP) Population	
Number of subjects	82	79	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
median	62		
full range (min-max)	31 to 77		
Gender categorical			
Units: Subjects			
Female	42		
Male	40		

End points

End points reporting groups

Reporting group title	Placebo/placebo arm (Arm 1)
Reporting group description:	
Placebo plus pemetrexed and carboplatin (4 cycles), pemetrexed (4 cycles), placebo plus pemetrexed (4 cycles).	
Reporting group title	Demcizumab/placebo arm (Arm 2)
Reporting group description:	
Demcizumab plus pemetrexed and carboplatin (4 cycles), pemetrexed (4 cycles), placebo plus pemetrexed (4 cycles).	
Reporting group title	Demcizumab/demcizumab arm (Arm 3)
Reporting group description:	
Demcizumab plus pemetrexed and carboplatin (4 cycles), pemetrexed (4 cycles), demcizumab plus pemetrexed (4 cycles).	
Subject analysis set title	Intent-to-treat (ITT) Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT Population comprised all subjects who were randomized. Subjects were analyzed as they were randomized.	
Subject analysis set title	Per-protocol (PP) Population
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population comprised all subjects who received at least 1 dose of demcizumab or placebo and had at least 1 postbaseline tumor assessment. Subjects were analyzed as they were treated. Efficacy, immunogenicity, and biomarker data was analyzed using the PP population as well as the ITT population.	

Primary: To compare the Investigator-assessed (RECIST) v1.1 response rate in the treatment arms

End point title	To compare the Investigator-assessed (RECIST) v1.1 response rate in the treatment arms
End point description:	
To compare the Investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 response rate (unconfirmed) in placebo/placebo arm to Demcizumab/placebo arm and demcizumab/demcizumab arm combined in subjects with first-line Stage IV NSCLC. The primary endpoint of response rate was based on Investigator-assessed BOR and was defined as the best unconfirmed response determined by RECIST version 1.1 recorded from the start of the treatment until disease progression in the following order of importance: CR, PR, SD, progressive disease (PD), not evaluable, or missing. The number and percentage of subjects in each disease response category (CR, PR, SD, PD, not evaluable, and missing) were summarized by treatment arm.	
End point type	Primary
End point timeframe:	
The time point of when a subject had progressed (censor = 0) their time to progression was determined by the date of progression (date of RECIST response assessment or date of death) minus start date + 1.	

End point values	Placebo/placebo arm (Arm 1)	Demcizumab/placebo arm (Arm 2)	Demcizumab/demcizumab arm (Arm 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	28	29	
Units: patients number				
Complete response (CR)	0	0	0	

Partial response (PR)	13	10	6	
Stable disease (SD)	10	14	15	
Progressive disease (PD)	2	4	5	
Not evaluable (NE)	0	0	0	
Missing	0	0	3	

Statistical analyses

Statistical analysis title	Kaplan-Meier model

Statistical analysis description:

The Kaplan-Meier method was used to estimate both the survival curves and the median survival time. The 95% CI for the median survival time was calculated. A p-value for treatment effect was generated using a stratified Cox proportional hazards model.

Comparison groups	Demcizumab/placebo arm (Arm 2) v Demcizumab/demcizumab arm (Arm 3) v Placebo/placebo arm (Arm 1)
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0401
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	0.95

Notes:

[1] - Based on RECIST v1.1. Response outcomes from an assessment done anytime less than Day 35 were considered as not evaluable unless the response assessment was PD.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All safety analyses were conducted on the safety population. Baseline for safety analysis was the last assessment prior to treatment.

Adverse event reporting additional description:

All reported AEs were mapped to standard MedDRA coding terms, grouped by system organ class (SOC) and preferred term (PT) and tabulated by treatment arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo/placebo arm (Arm 1)

Reporting group description:

Placebo plus pemetrexed and carboplatin (4 cycles), pemetrexed (4 cycles), placebo plus pemetrexed (4 cycles).

Reporting group title	Demcizumab/placebo arm (Arm 2)

Reporting group description:

Demcizumab plus pemetrexed and carboplatin (4 cycles), Pemetrexed (4 cycles), placebo plus pemetrexed (4 cycles).

Reporting group title	Demcizumab/demcizumab arm (Arm 3)

Reporting group description:

Demcizumab plus pemetrexed and carboplatin (4 cycles), pemetrexed (4 cycles), demcizumab plus pemetrexed (4 cycles).

Serious adverse events	Placebo/placebo arm (Arm 1)	Demcizumab/placebo arm (Arm 2)	Demcizumab/demcizumab arm (Arm 3)
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 25 (24.00%)	11 / 28 (39.29%)	15 / 29 (51.72%)
number of deaths (all causes)	1	2	2
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 28 (0.00%)	0 / 29 (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
Metastases to liver			
subjects affected / exposed	0 / 25 (0.00%)	1 / 28 (3.57%)	0 / 29 (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
Vascular disorders			

Hypertension			
subjects affected / exposed	0 / 25 (0.00%)	1 / 28 (3.57%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 28 (0.00%)	2 / 29 (6.90%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 28 (0.00%)	2 / 29 (6.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 25 (0.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 28 (3.57%)	0 / 29 (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
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 25 (0.00%)	1 / 28 (3.57%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 25 (0.00%)	1 / 28 (3.57%)	0 / 29 (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
Pulmonary hypertension			
subjects affected / exposed	0 / 25 (0.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 25 (0.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Ejection fraction decreased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 28 (3.57%)	0 / 29 (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
Platelet count decreased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 28 (3.57%)	0 / 29 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 25 (4.00%)	0 / 28 (0.00%)	0 / 29 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Cervical cord compression			
subjects affected / exposed	1 / 25 (4.00%)	0 / 28 (0.00%)	0 / 29 (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
Headache			
subjects affected / exposed	0 / 25 (0.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 28 (3.57%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 28 (0.00%)	0 / 29 (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
Neutropenia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 28 (0.00%)	0 / 29 (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
Thrombocytopenia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 28 (0.00%)	0 / 29 (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
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	2 / 25 (8.00%)	1 / 28 (3.57%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 25 (0.00%)	1 / 28 (3.57%)	2 / 29 (6.90%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 25 (4.00%)	0 / 28 (0.00%)	0 / 29 (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	0 / 25 (0.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 28 (0.00%)	0 / 29 (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
Vomiting			
subjects affected / exposed	0 / 25 (0.00%)	1 / 28 (3.57%)	0 / 29 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 25 (0.00%)	1 / 28 (3.57%)	0 / 29 (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
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	1 / 25 (4.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 28 (3.57%)	0 / 29 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 28 (7.14%)	3 / 29 (10.34%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 28 (0.00%)	0 / 29 (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
Gastroenteritis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 28 (0.00%)	0 / 29 (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
Influenza			
subjects affected / exposed	0 / 25 (0.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 28 (3.57%)	0 / 29 (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
Respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 25 (0.00%)	1 / 28 (3.57%)	0 / 29 (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

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

Non-serious adverse events	Placebo/placebo arm (Arm 1)	Demcizumab/placebo arm (Arm 2)	Demcizumab/demcizumab arm (Arm 3)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 25 (100.00%)	28 / 28 (100.00%)	29 / 29 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 25 (16.00%)	14 / 28 (50.00%)	12 / 29 (41.38%)
occurrences (all)	4	14	12
Hypotension			
subjects affected / exposed	4 / 25 (16.00%)	2 / 28 (7.14%)	3 / 29 (10.34%)
occurrences (all)	4	2	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	15 / 25 (60.00%)	16 / 28 (57.14%)	12 / 29 (41.38%)
occurrences (all)	15	16	12
Asthenia			
subjects affected / exposed	8 / 25 (32.00%)	10 / 28 (35.71%)	9 / 29 (31.03%)
occurrences (all)	8	28	29
Pyrexia			
subjects affected / exposed	4 / 25 (16.00%)	6 / 28 (21.43%)	9 / 29 (31.03%)
occurrences (all)	4	6	9
Oedema peripheral			
subjects affected / exposed	5 / 25 (20.00%)	4 / 28 (14.29%)	1 / 29 (3.45%)
occurrences (all)	5	4	1
Malaise			
subjects affected / exposed	3 / 25 (12.00%)	2 / 28 (7.14%)	1 / 29 (3.45%)
occurrences (all)	3	2	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	6 / 25 (24.00%)	7 / 28 (25.00%)	9 / 29 (31.03%)
occurrences (all)	6	7	9

Cough			
subjects affected / exposed	6 / 25 (24.00%)	8 / 28 (28.57%)	5 / 29 (17.24%)
occurrences (all)	6	8	5
Epistaxis			
subjects affected / exposed	2 / 25 (8.00%)	4 / 28 (14.29%)	5 / 29 (17.24%)
occurrences (all)	2	4	5
Haemoptysis			
subjects affected / exposed	3 / 25 (12.00%)	1 / 28 (3.57%)	3 / 29 (10.34%)
occurrences (all)	3	1	3
Rhinorrhoea			
subjects affected / exposed	5 / 25 (20.00%)	0 / 28 (0.00%)	2 / 29 (6.90%)
occurrences (all)	5	0	2
Dyspnoea exertional			
subjects affected / exposed	2 / 25 (8.00%)	3 / 28 (10.71%)	1 / 29 (3.45%)
occurrences (all)	2	3	1
Productive cough			
subjects affected / exposed	2 / 25 (8.00%)	2 / 28 (7.14%)	2 / 29 (6.90%)
occurrences (all)	2	2	2
Pulmonary embolism			
subjects affected / exposed	2 / 25 (8.00%)	2 / 28 (7.14%)	1 / 29 (3.45%)
occurrences (all)	2	2	1
Pulmonary hypertension			
subjects affected / exposed	0 / 25 (0.00%)	4 / 28 (14.29%)	1 / 29 (3.45%)
occurrences (all)	0	4	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 25 (20.00%)	5 / 28 (17.86%)	7 / 29 (24.14%)
occurrences (all)	5	5	7
Anxiety			
subjects affected / exposed	3 / 25 (12.00%)	2 / 28 (7.14%)	1 / 29 (3.45%)
occurrences (all)	3	2	1
Investigations			
Brain natriuretic peptide increased			
subjects affected / exposed	0 / 25 (0.00%)	8 / 28 (28.57%)	6 / 29 (20.69%)
occurrences (all)	0	8	6
Alanine aminotransferase increased			

subjects affected / exposed	6 / 25 (24.00%)	4 / 28 (14.29%)	3 / 29 (10.34%)
occurrences (all)	6	4	3
Platelet count decreased			
subjects affected / exposed	4 / 25 (16.00%)	4 / 28 (14.29%)	2 / 29 (6.90%)
occurrences (all)	4	4	2
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 25 (12.00%)	3 / 28 (10.71%)	2 / 29 (6.90%)
occurrences (all)	3	3	2
Neutrophil count decreased			
subjects affected / exposed	3 / 25 (12.00%)	3 / 28 (10.71%)	2 / 29 (6.90%)
occurrences (all)	3	3	2
Blood creatinine increased			
subjects affected / exposed	2 / 25 (8.00%)	3 / 28 (10.71%)	1 / 29 (3.45%)
occurrences (all)	2	3	1
Weight decreased			
subjects affected / exposed	2 / 25 (8.00%)	2 / 28 (7.14%)	1 / 29 (3.45%)
occurrences (all)	2	2	1
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	3 / 25 (12.00%)	3 / 28 (10.71%)	1 / 29 (3.45%)
occurrences (all)	3	3	1
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 25 (28.00%)	11 / 28 (39.29%)	7 / 29 (24.14%)
occurrences (all)	7	11	7
Dizziness			
subjects affected / exposed	8 / 25 (32.00%)	9 / 28 (32.14%)	2 / 29 (6.90%)
occurrences (all)	8	9	2
Dysgeusia			
subjects affected / exposed	8 / 25 (32.00%)	3 / 28 (10.71%)	2 / 29 (6.90%)
occurrences (all)	8	3	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 25 (44.00%)	11 / 28 (39.29%)	8 / 29 (27.59%)
occurrences (all)	11	11	8
Neutropenia			

subjects affected / exposed	5 / 25 (20.00%)	6 / 28 (21.43%)	5 / 29 (17.24%)
occurrences (all)	5	6	5
Thrombocytopenia			
subjects affected / exposed	3 / 25 (12.00%)	3 / 28 (10.71%)	5 / 29 (17.24%)
occurrences (all)	3	3	5
Febrile neutropenia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 28 (3.57%)	2 / 29 (6.90%)
occurrences (all)	2	1	2
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 25 (0.00%)	4 / 28 (14.29%)	1 / 29 (3.45%)
occurrences (all)	0	4	1
Eye disorders			
Lacrimation increased			
subjects affected / exposed	3 / 25 (12.00%)	5 / 28 (17.86%)	3 / 29 (10.34%)
occurrences (all)	3	5	3
Dry eye			
subjects affected / exposed	3 / 25 (12.00%)	3 / 28 (10.71%)	0 / 29 (0.00%)
occurrences (all)	3	3	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	18 / 25 (72.00%)	18 / 28 (64.29%)	14 / 29 (48.28%)
occurrences (all)	18	18	14
Constipation			
subjects affected / exposed	15 / 25 (60.00%)	11 / 28 (39.29%)	11 / 29 (37.93%)
occurrences (all)	15	11	11
Vomiting			
subjects affected / exposed	9 / 25 (36.00%)	8 / 28 (28.57%)	11 / 29 (37.93%)
occurrences (all)	9	8	11
Diarrhoea			
subjects affected / exposed	7 / 25 (28.00%)	6 / 28 (21.43%)	13 / 29 (44.83%)
occurrences (all)	7	6	13
Stomatitis			
subjects affected / exposed	5 / 25 (20.00%)	4 / 28 (14.29%)	5 / 29 (17.24%)
occurrences (all)	5	4	5
Abdominal pain			

subjects affected / exposed	5 / 25 (20.00%)	4 / 28 (14.29%)	4 / 29 (13.79%)
occurrences (all)	5	4	4
Dyspepsia			
subjects affected / exposed	1 / 25 (4.00%)	2 / 28 (7.14%)	4 / 29 (13.79%)
occurrences (all)	1	2	4
Abdominal distension			
subjects affected / exposed	4 / 25 (16.00%)	1 / 28 (3.57%)	0 / 29 (0.00%)
occurrences (all)	4	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 25 (16.00%)	7 / 28 (25.00%)	6 / 29 (20.69%)
occurrences (all)	4	7	6
Alopecia			
subjects affected / exposed	3 / 25 (12.00%)	1 / 28 (3.57%)	1 / 29 (3.45%)
occurrences (all)	3	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 25 (16.00%)	4 / 28 (14.29%)	6 / 29 (20.69%)
occurrences (all)	4	4	6
Back pain			
subjects affected / exposed	6 / 25 (24.00%)	3 / 28 (10.71%)	2 / 29 (6.90%)
occurrences (all)	6	3	2
Musculoskeletal chest pain			
subjects affected / exposed	3 / 25 (12.00%)	4 / 28 (14.29%)	2 / 29 (6.90%)
occurrences (all)	3	4	2
Neck pain			
subjects affected / exposed	3 / 25 (12.00%)	2 / 28 (7.14%)	1 / 29 (3.45%)
occurrences (all)	3	2	1
Myalgia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 28 (3.57%)	2 / 29 (6.90%)
occurrences (all)	2	1	2
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 25 (4.00%)	3 / 28 (10.71%)	4 / 29 (13.79%)
occurrences (all)	1	3	4
Urinary tract infection			

subjects affected / exposed	1 / 25 (4.00%)	3 / 28 (10.71%)	1 / 29 (3.45%)
occurrences (all)	1	3	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 25 (20.00%)	11 / 28 (39.29%)	9 / 29 (31.03%)
occurrences (all)	5	11	9
Dehydration			
subjects affected / exposed	2 / 25 (8.00%)	3 / 28 (10.71%)	4 / 29 (13.79%)
occurrences (all)	2	3	4
Hyperglycaemia			
subjects affected / exposed	1 / 25 (4.00%)	5 / 28 (17.86%)	2 / 29 (6.90%)
occurrences (all)	1	5	2
Hypomagnesaemia			
subjects affected / exposed	3 / 25 (12.00%)	2 / 28 (7.14%)	2 / 29 (6.90%)
occurrences (all)	3	2	2
Hyperkalaemia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 28 (3.57%)	3 / 29 (10.34%)
occurrences (all)	2	1	3
Hypokalaemia			
subjects affected / exposed	4 / 25 (16.00%)	1 / 28 (3.57%)	0 / 29 (0.00%)
occurrences (all)	4	1	0
Hypophosphataemia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 28 (3.57%)	2 / 29 (6.90%)
occurrences (all)	2	1	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported