Clinical trial results:
Open-Label Access Protocol of Denosumab for Subjects with Advanced Cancer

Summary

EudraCT number	2011-002114-36
Trial protocol	HU CZ AT FR ES PL BE LV LT IT
Global end of trial date	10 August 2018

Results information

Result version number	v1 (current)
This version publication date	17 August 2019
First version publication date	17 August 2019

Trial information

Trial identification

Sponsor protocol code	20110113

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01419717
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to facilitate the access of denosumab until denosumab was approved and available for sale for subjects with advanced cancer who had participated in a denosumab phase 3 study.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
The protocol, proposed informed consent form, other written subject information, and any proposed advertising material were submitted to the Independent Ethics Committee/Institutional Review Board (IEC/IRB) for written approval before recruitment of subjects into the study and shipment of Amgen investigational product.
Before a subject's participation in the clinical study, the investigator was responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products were administered.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Latvia: 8
Country: Number of subjects enrolled	Lithuania: 8
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Ukraine: 5
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Brazil: 16

Country: Number of subjects enrolled	Argentina: 8
Country: Number of subjects enrolled	Peru: 6
Country: Number of subjects enrolled	Panama: 1
Country: Number of subjects enrolled	Japan: 15
Country: Number of subjects enrolled	South Africa: 1
Worldwide total number of subjects	129
EEA total number of subjects	58

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)	60
From 65 to 84 years	64
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 65 centers in Europe, Latin America, Japan, and South Africa. Participants were enrolled from 22 November 2011 to 27 October 2014.

Pre-assignment

Screening details:

Adults with advanced cancer who had been previously enrolled in an Amgen denosumab phase 3 study and had participated in the open-label extension portion of that study were eligible to enroll in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Denosumab

Arm description:

Participants were offered 120 milligrams of denosumab injected subcutaneously every 4 weeks until denosumab was approved and available for sale.

Arm type	Experimental
Investigational medicinal product name	Denosumab
Investigational medicinal product code	AMG 162
Other name	Xgeva
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once every 4 weeks (Q4W) at a dose of 120 mg.

Number of subjects in period 1	Denosumab
Started	129
Received Denosumab	128
Completed	4
Not completed	125
Adverse event, serious fatal	17
Consent withdrawn by subject	10
Adverse event, non-fatal	19
Other	4
Administrative Decision	1
Lost to follow-up	2
Protocol-specified Criteria	62
Disease Progression	9

Noncompliance	1

Baseline characteristics

Reporting groups	
Reporting group title	Denosumab
Reporting group description:	
Participants were offered 120 milligrams of denosumab injected subcutaneously every 4 weeks until denosumab was approved and available for sale.	

Reporting group values	Denosumab	Total	
Number of subjects	129	129	
Age, Customized Units: Subjects			
18 - 64 years	60	60	
65 - 74 years	36	36	
75 - 84 years	28	28	
≥ 85 years	5	5	
Age Continuous Units: years			
arithmetic mean	65.74		
standard deviation	± 11.48	-	
Sex: Female, Male Units: Subjects			
Female	97	97	
Male	32	32	
Race/Ethnicity, Customized Units: Subjects			
White	103	103	
Asian	15	15	
Black or African American	6	6	
Other	4	4	
Unknown	1	1	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	28	28	
Not Hispanic or Latino	101	101	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Denosumab

Reporting group description:

Participants were offered 120 milligrams of denosumab injected subcutaneously every 4 weeks until denosumab was approved and available for sale.

Primary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events[1]

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a clinical trial participant. The event does not necessarily have a causal relationship with study treatment. Each AE was graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, where
Grade 1 = Mild AE
Grade 2 = Moderate AE
Grade 3 = Severe AE
Grade 4 = Life-threatening or disabling AE
Grade 5 = Death related to AE.
Treatment-related adverse events (TRAEs) includes events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product.

End point type	Primary

End point timeframe:

From first dose of denosumab in Study 20110113 to end of study. Median (minimum, maximum) time on study was 13.93 (0.0, 74.7) months.

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: The statistical analysis in this study was entirely descriptive; no formal statistical hypothesis was tested or estimated.

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	128[2]			
Units: participants				
All adverse events	98			
Serious adverse events	45			
AE leading to discontinuation of denosumab	28			
AE leading to discontinuation from study	22			
Fatal adverse events	18			
AE grade 3, 4, or 5	46			
Treatment-related adverse event	26			
Treatment-related serious adverse event	10			
TRAE leading to discontinuation of denosumab	18			
TRAE leading to discontinuation from study	16			
Treatment-related fatal adverse events	0			
Treatment-related AE grade 3, 4, or 5	8			

Notes:

[2] - Participants who received at least 1 dose of denosumab in study 20110113.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anti-denosumab Binding Antibodies

End point title	Number of Participants with Anti-denosumab Binding Antibodies

End point description:

A blood sample was collected at the end of study visit for the measurement of anti-denosumab binding antibodies.

End point type	Secondary

End point timeframe:

Assessed at end of study; the median (minimum, maximum) time on study for all enrolled participants was 13.9 (0.0, 74.7) months.

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	86[3]			
Units: participants	0			

Notes:

[3] - Participants who received at least 1 dose of denosumab and with at least 1 antibody result.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of denosumab in Study 20110113 to end of study. Median (minimum, maximum) time on study was 13.93 (0.0, 74.7) months

Adverse event reporting additional description:

Participants who received at least one dose of denosumab.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Denosumab

Reporting group description:

Participants received 120 milligrams of denosumab injected subcutaneously every 4 weeks until denosumab was approved and available for sale.

Serious adverse events	Denosumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 128 (35.16%)		
number of deaths (all causes)	18		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	2 / 128 (1.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Cardiac myxoma			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to liver			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Neoplasm malignant			

subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Disease progression				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
General physical health deterioration				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Respiratory, thoracic and mediastinal disorders				
Acute pulmonary oedema				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	3 / 128 (2.34%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			

Pleurisy				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Arrhythmia				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiopulmonary failure				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Nervous system disorders			
Hemiparesis			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Paraplegia			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiculopathy			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vertebrobasilar insufficiency			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 128 (2.34%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	2 / 128 (1.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 128 (1.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ascites			

subjects affected / exposed	2 / 128 (1.56%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	2 / 128 (1.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Melaena			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 128 (1.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue			

disorders			
Muscle spasms			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis of jaw			
subjects affected / exposed	7 / 128 (5.47%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess jaw			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myelitis			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	3 / 128 (2.34%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	4 / 128 (3.13%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		

Pulpitis dental			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	2 / 128 (1.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Hypoglycaemia			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Denosumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 128 (51.56%)		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 128 (6.25%)		
occurrences (all)	11		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	15 / 128 (11.72%)		
occurrences (all)	18		

Fatigue subjects affected / exposed occurrences (all)	12 / 128 (9.38%) 18		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 9 / 128 (7.03%) 10 11 / 128 (8.59%) 17 15 / 128 (11.72%) 23 9 / 128 (7.03%) 11 11 / 128 (8.59%) 16		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 7 / 128 (5.47%) 12		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Osteonecrosis of jaw subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 15 / 128 (11.72%) 26 16 / 128 (12.50%) 18 8 / 128 (6.25%) 8 13 / 128 (10.16%) 14		

Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 14 / 128 (10.94%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2013	Summary of changes: • Clarify that serious adverse events must be reported within 24 hours • Clarify how serious adverse events reported to Amgen will be reported to regulators and investigators • Provide lactation notification worksheet in the protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported