Clinical trial results:
Long-term Safety Follow-up of Subjects With Giant Cell Tumor of Bone Treated With Denosumab in Study 20062004

Summary

EudraCT number	2017-001758-32
Trial protocol	SE GB ES PL FR IT
Global end of trial date	27 July 2023

Results information

Result version number	v1
This version publication date	17 December 2023
First version publication date	17 December 2023

Trial information

Trial identification

Sponsor protocol code	20140114

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03301857
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States,
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	27 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Study 20140114 continued to follow subjects with Giant Cell Tumor of Bone (GCTB) who were treated in Study 20062004 and remained on the study at the completion of Study 20062004 for an additional 5 years on long-term safety follow up.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines. Essential documents will be retained in accordance with ICH GCP. The study sponsor declares that the information provided in this report is an accurate representation of the data captured and analyses performed for this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 November 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 31
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Sweden: 3
Worldwide total number of subjects	85
EEA total number of subjects	46

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)	2
Adults (18-64 years)	78
From 65 to 84 years	4
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects with GCTB were recruited across 8 countries (Australia, Italy, France, Poland, Spain, Sweden, the United Kingdom of Great Britain and Northern Ireland, and the United States) between November 2017 and July 2023.

Pre-assignment

Screening details:

Study 20140114 was a prospective, multicenter, open label, phase 4 study that provided long term safety follow up for participants who completed Study 20062004 and provided consent to enroll in Study 20140114.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Exposed to Investigational Product (IP)

Arm description:

Participants who received denosumab at the conclusion of Study 20062004 continued receiving denosumab at the current dose (120 mg every 4 weeks [Q4W] subcutaneous injection [SC]) and schedule at the investigator's discretion.

Arm type	Experimental
Investigational medicinal product name	Denosumab
Investigational medicinal product code	
Other name	XGEVA
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

120 mg Q4W SC

Arm title	Not Exposed to IP

Arm description:

Participants who completed denosumab treatment in Study 20062004 and were in the safety follow up at the conclusion of Study 20062004 continued in long term safety follow up in this study (Study 20140114), and did not received denosumab.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Exposed to Investigational Product (IP)	Not Exposed to IP
Started	51	34
Completed	29	26
Not completed	22	8
Consent withdrawn by subject	12	4
Decision by Sponsor	6	-

Death	-	2
Lost to follow-up	4	2

Baseline characteristics

Reporting groups	
Reporting group title	Exposed to Investigational Product (IP)
Reporting group description:	
Participants who received denosumab at the conclusion of Study 20062004 continued receiving denosumab at the current dose (120 mg every 4 weeks [Q4W] subcutaneous injection [SC]) and schedule at the investigator's discretion.	
Reporting group title	Not Exposed to IP
Reporting group description:	
Participants who completed denosumab treatment in Study 20062004 and were in the safety follow up at the conclusion of Study 20062004 continued in long term safety follow up in this study (Study 20140114), and did not received denosumab.	

Reporting group values	Exposed to Investigational Product (IP)	Not Exposed to IP	Total
Number of subjects	51	34	85
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)	1	1	2
Adults (18-64 years)	48	30	78
From 65-84 years	2	2	4
85 years and over	0	1	1
Age Continuous Units: years			
arithmetic mean	42.4	46.7	
standard deviation	± 12.8	± 15.1	-
Gender Categorical Units: Subjects			
Female	32	23	55
Male	19	11	30
Race Units: Subjects			
White	35	31	66
Other	10	0	10
Black (or African American)	4	3	7
Asian	2	0	2
Ethnicity Units: Subjects			
Hispanic/Latino	13	10	23
Not Hispanic/Latino	38	24	62

End points

End points reporting groups

Reporting group title	Exposed to Investigational Product (IP)

Reporting group description:

Participants who received denosumab at the conclusion of Study 20062004 continued receiving denosumab at the current dose (120 mg every 4 weeks [Q4W] subcutaneous injection [SC]) and schedule at the investigator's discretion.

Reporting group title	Not Exposed to IP

Reporting group description:

Participants who completed denosumab treatment in Study 20062004 and were in the safety follow up at the conclusion of Study 20062004 continued in long term safety follow up in this study (Study 20140114), and did not received denosumab.

Primary: Number of Participants Experiencing Adverse Events of Interest (EOI) in Participants with GCTB Treated with Denosumab in Study 20062004

End point title	Number of Participants Experiencing Adverse Events of Interest (EOI) in Participants with GCTB Treated with Denosumab in Study 20062004[1]

End point description:

EOI assessed in the study were to be assessed for signs and symptoms of the adverse EOI of osteonecrosis of the jaw (ONJ), malignancy (including malignancy in GCTB), atypical femoral fracture (AFF), hypocalcemia, hypercalcemia after treatment discontinuation, pregnancy and lactation (if occurring on treatment or within 5 months of last dose of denosumab).

End point type	Primary

End point timeframe:

Up to Approximately 5 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: This endpoint was specified only for the IMP-exposed group.

End point values	Exposed to Investigational Product (IP)	Not Exposed to IP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[2]	34		
Units: Count of Participants				
Adj+ Osteonecrosis of jaw - Adverse Events (AE)	3	0		
Malignancy, including malignancy in GCTB - AE	6	1		
Adj+ Atypical femoral fracture - AE	2	0		
Hypocalcemia - AE	3	0		
Hypocalcemia after treatment end - AE	0	0		
Pregnancy and lactation	0	0		

Notes:

[2] - One pregnancy in female partners of male subjects treated with denosumab was reported

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing Treatment-emergent Adverse Events (TEAE) for Participants who Received Denosumab.

End point title	Number of Participants Experiencing Treatment-emergent Adverse Events (TEAE) for Participants who Received Denosumab.[3]

End point description:

An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. An adverse event is considered as treatment emergent if the adverse event occurs during the time period from the first dose of investigational product (IP) in this study through last dose of IP plus 30 days. TEAEs related to IP include only TEAEs for which the investigator indicated there was a reasonable possibility they may have been caused by IP.

End point type	Secondary

End point timeframe:

Up to Approximately 5 Years

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was specified only for the IMP-exposed group.

End point values	Exposed to Investigational Product (IP)			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: Count of Participants				
All TEAEs	47			
Serious TEAEs	8			
Fatal TEAEs	0			
TEAEs leading to IP discontinuation	9			
CTCAE Grade 3, 4, or 5	16			
All TEAEs related to IP	14			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing Serious Adverse Events

End point title	Number of Participants Experiencing Serious Adverse Events

End point description:

A Serious Adverse Event is defined as any untoward medical occurrence that meets at least 1 of the following serious criteria:
- Results in death (fatal)
- Immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Other medically important serious event

End point type	Secondary

End point timeframe:

From Date of Signing ICF up to Approximately 5 Years

End point values	Exposed to Investigational Product (IP)	Not Exposed to IP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	34		
Units: Count of Participants				
Number of Participants Reporting Serious AE	11	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Disease Progression or Recurrence of GCTB

End point title	Number of Participants with Disease Progression or Recurrence of GCTB

End point description:

Disease progression or recurrence is defined as the best post-baseline response of progressive disease (PD) without any post-baseline complete response (CR) /partial response (PR) /stable disease (SD) or a post-baseline response of PD following a postbaseline CR/PR/SD. PD is defined as the response of progressive disease, locally recurrent disease or distant recurrence as captured in the Disease Status page of the Case Report Form.

End point type	Secondary

End point timeframe:

Up to Approximately 5 Years

End point values	Exposed to Investigational Product (IP)	Not Exposed to IP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50[4]	33[5]		
Units: Count of Participants				
Disease Progression or Recurrence	5	3		

Notes:

[4] - Number of subjects analyzed: subjects who had at least one post-baseline disease status evaluation.

[5] - Number of subjects analyzed: subjects who had at least one post-baseline disease status evaluation.

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of GCTB Interventions

End point title	Summary of GCTB Interventions

End point description:

Data from the full analysis set (FAS) which included all enrolled subjects (from Study 20062004) who provided informed consent and had a non-missing enrollment date in this study.

End point type	Secondary

End point timeframe:

Up to Approximately 5 Years

End point values	Exposed to Investigational Product (IP)	Not Exposed to IP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	34		
Units: Count of Participants				
Surgery for GCTB - Yes	0	0		
Surgery for GCTB - No	51	34		
Chemotherapy or Other Therapeutic Agents - Yes	0	1		
Chemotherapy or Other Therapeutic Agents - No	51	33		
Embolization - Yes	0	0		
Embolization - No	51	34		
Interferon - Yes	0	0		
Interferon - No	51	34		
Radiotherapy - Yes	0	0		
Radiotherapy - No	51	34		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE from 1st dose to last dose+30 days in the study. Fatality from 1st dose to end-of-study (EOS) (approximately 5 years); two deaths from not dosed subjects are excluded. Median on IP: 53.4 Months.

Adverse event reporting additional description:

20140114 Primary

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Exposed to IP

Reporting group description:

Participants who received denosumab at the conclusion of Study 20062004 continued receiving denosumab at the current dose (120 mg Q4W SC) and schedule at the investigator's discretion.

Serious adverse events	Exposed to IP		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 51 (15.69%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Osteosarcoma			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Patella fracture			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Anaemia				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Gastrointestinal obstruction				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anal fistula				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Osteonecrosis of jaw				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Myositis				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Sepsis				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Medical device site infection				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral pericarditis				

subjects affected / exposed	1 / 51 (1.96%)		
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	Exposed to IP		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 51 (76.47%)		
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	5		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	8 / 51 (15.69%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	5		
Dyspnoea			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		

Musculoskeletal and connective tissue disorders			
Osteonecrosis of jaw			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	7		
Myalgia			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Back pain			
subjects affected / exposed	7 / 51 (13.73%)		
occurrences (all)	9		
Arthralgia			
subjects affected / exposed	8 / 51 (15.69%)		
occurrences (all)	13		
Pain in extremity			
subjects affected / exposed	8 / 51 (15.69%)		
occurrences (all)	12		
Infections and infestations			
COVID-19			
subjects affected / exposed	7 / 51 (13.73%)		
occurrences (all)	7		
Gingivitis			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Sinusitis			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	7		
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 November 2017	• Clarified guidance to investigators about monitoring subjects for hypercalcemia upon discontinuation or interruption of investigational product. • Added month 60 to the Schedule of Assessments for clarity.
23 January 2018	The objective of Study 20140114 was to continue to follow subjects with GCTB who were treated in Study 20062004. A minor language of inclusion criterion 101 was updated to clarify that: • To be considered potentially eligible for this study, a subject must had participated in the parent 20062004 study and had completed participation in that study, and • A subject could not be concurrently enrolled to Study 20062004 and Study 20140114; which was not clear according to the original protocol inclusion criterion 101.
23 August 2018	Schedule of Activities • Changed the interval between last dose of denosumab and the EOT in person clinic visit. Study Treatments • Added detail to denosumab dosing instructions. Serious Adverse Events • Clarified procedure for reporting serious adverse events and/or events of interest for subjects who experienced a treatment gap of more than 30 days between the EOS visit of Study 20062004 and signing the ICF for Study 20140114. Study Rationale • Clarified that Study 20062004 ended in May 2018, as the study was extended by a year. • Clarified that subjects with surgically salvageable disease, treatment continued until surgery for complete resection and for approximately 6 months after surgery, as aligned to the 20062004 study. Overall Design • Clarified that the EOS visit for all subjects was at 5 years. Cohort A subjects on investigational product had an EOS visit conducted 30 days after the last dose of investigational product (EOT visit) if received investigational product at the 5-year time point. Lost to Follow up • Clarified that investigators will not search publicly available records to ascertain survival status when a subject is lost to follow-up. Discontinuation of Study Treatment • Clarified that upon discontinuation, subject's risk for vertebral fragility fractures were evaluated. This language was being added to align language with the core data sheet.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported