



## 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          | v2 (current)     |
| This version publication date  | 18 April 2024    |
| First version publication date | 17 December 2023 |
| Version creation reason        |                  |

#### 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,<br>MedInfoInternational@amgen.com |
| Scientific contact           | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH,<br>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:

To evaluate adverse events (AEs) of interest (EOI) in subjects with GCTB treated with denosumab in Study 20062004.

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:

All participants were adequately supplemented with calcium and vitamin D (at least 500 mg of calcium and 400 IU of vitamin D), except in the case of pre-existing hypercalcemia.

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:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| 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:

Participants 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                                     |
| <b>Arm title</b>             | 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

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | 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                |
| Received Denosumab             | 51                                      | 0 <sup>[1]</sup>  |
| 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 |

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Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Intermediate milestone represents the number of participants who were exposed to the IP, and helps clarifying that only participants in the first arm received denosumab during this study.

## 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<br>Units: Participants             |                                         |                   |       |
| 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<br>Units: years                     |                                         |                   |       |
| arithmetic mean                                    | 42.4                                    | 46.7              | -     |
| standard deviation                                 | ± 12.8                                  | ± 15.1            |       |
| Gender Categorical<br>Units: Participants          |                                         |                   |       |
| Female                                             | 32                                      | 23                | 55    |
| Male                                               | 19                                      | 11                | 30    |
| Race<br>Units: Subjects                            |                                         |                   |       |
| White                                              | 35                                      | 31                | 66    |
| Other                                              | 10                                      | 0                 | 10    |
| Black (or African American)                        | 4                                       | 3                 | 7     |
| Asian                                              | 2                                       | 0                 | 2     |
| Ethnicity<br>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:<br>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:<br>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 AEs EOI

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Number of Participants Experiencing AEs EOI <sup>[1]</sup> |
| End point description:<br>EOIs assessed in the study were signs and symptoms 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 during treatment or within 5 months of the last dose of denosumab). Hypocalcemia includes events that occurred after 30 days following the last dose of IP and includes TEAEs only. Other EOIs encompass all events from signing the informed consent to the end of the study (approximately 5 years). |                                                            |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Primary                                                    |
| End point timeframe:<br>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: No additional statistical analysis was pre-specified for this endpoint.

| 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             |                                         |                   |  |  |
| Adj + ONJ                                | 3                                       | 0                 |  |  |
| Malignancy, including malignancy in GCTB | 6                                       | 1                 |  |  |
| Adj + AFF                                | 2                                       | 0                 |  |  |
| Hypocalcemia                             | 3                                       | 0                 |  |  |
| Hypocalcemia after treatment end         | 0                                       | 0                 |  |  |
| Pregnancy and lactation                  | 0                                       | 0                 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Experiencing Treatment-emergent Adverse

## Events (TEAE)

|                 |                                                                                             |
|-----------------|---------------------------------------------------------------------------------------------|
| End point title | Number of Participants Experiencing Treatment-emergent Adverse Events (TEAE) <sup>[2]</sup> |
|-----------------|---------------------------------------------------------------------------------------------|

End point description:

An AE is any untoward medical occurrence in a clinical study participant irrespective of a causal relationship with the study treatment. An AE is considered as treatment-emergent if the AE occurs during the time period from the first dose of 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. AEs were graded (grade 3 [severe or medically significant but not immediately life-threatening], 4 [life-threatening], and 5 [death related to the AE]) using the Common Terminology Criteria for Adverse Events (CTCAE). Data from FAS which included all enrolled participants (from study 20062004) who provided informed consent and had a non-missing enrolment date in this study.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Approximately 5 Years

Notes:

[2] - 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: For this endpoint it was pre-specified to report results for the investigational arm only.

|                                     |                                         |  |  |  |
|-------------------------------------|-----------------------------------------|--|--|--|
| <b>End point values</b>             | 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 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 post-baseline CR/PR/SD. PD is defined as the response of progressive disease, locally recurrent disease or distant recurrence. CR is defined as no evidence of disease following surgical resection while on study 20062004. PR is defined as no new lesion or disease progression while enrolled in study 20062004. SD is defined as local disease progression/recurrence or distant metastatic disease while on study 20062004. Data from FAS which included all enrolled participants (from study 20062004) who provided informed consent and had a non-missing enrolment 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       | 50                                      | 33                |  |  |
| Units: Count of Participants      |                                         |                   |  |  |
| Disease Progression or Recurrence | 5                                       | 3                 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Receiving GCTB Interventions

|                                                                                                                                                                                                                                                               |                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| End point title                                                                                                                                                                                                                                               | Number of Participants Receiving GCTB Interventions |
| End point description:                                                                                                                                                                                                                                        |                                                     |
| GCTB interventions include: surgery, chemotherapy, embolization, interferon, and radiotherapy. Data from FAS which included all enrolled participants (from study 20062004) who provided informed consent and had a non-missing enrolment 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                         | 1                                       | 3                 |  |  |
| Chemotherapy or Other Therapeutic Agents | 0                                       | 2                 |  |  |
| Embolization                             | 0                                       | 0                 |  |  |
| Interferon                               | 0                                       | 0                 |  |  |
| Radiotherapy                             | 0                                       | 0                 |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Approximately 5 years

Adverse event reporting additional description:

Data from FAS which included all enrolled participants (from study 20062004) who provided informed consent and had a non-missing enrolment date in this study.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 26.0 |
|--------------------|------|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Exposed to IP |
|-----------------------|---------------|

Reporting group description: -

| 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                      |                 |  |  |
| 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           |  |  |
| 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           |  |  |
| 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 |                |  |  |
| Myositis                                        |                |  |  |
| subjects affected / exposed                     | 1 / 51 (1.96%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| 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          |  |  |
| 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 %

|                                                       |                  |  |  |
|-------------------------------------------------------|------------------|--|--|
| <b>Non-serious adverse events</b>                     | 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                           | 3 / 51 (5.88%)   |  |  |
| 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       |                  |  |  |
| Dyspnoea                                              |                  |  |  |
| subjects affected / exposed                           | 3 / 51 (5.88%)   |  |  |
| occurrences (all)                                     | 3                |  |  |
| Cough                                                 |                  |  |  |
| subjects affected / exposed                           | 5 / 51 (9.80%)   |  |  |
| occurrences (all)                                     | 5                |  |  |
| Musculoskeletal and connective tissue                 |                  |  |  |

|                                    |                 |  |  |
|------------------------------------|-----------------|--|--|
| disorders                          |                 |  |  |
| Arthralgia                         |                 |  |  |
| subjects affected / exposed        | 8 / 51 (15.69%) |  |  |
| occurrences (all)                  | 13              |  |  |
| Back pain                          |                 |  |  |
| subjects affected / exposed        | 7 / 51 (13.73%) |  |  |
| occurrences (all)                  | 9               |  |  |
| Myalgia                            |                 |  |  |
| subjects affected / exposed        | 4 / 51 (7.84%)  |  |  |
| occurrences (all)                  | 4               |  |  |
| Osteonecrosis of jaw               |                 |  |  |
| subjects affected / exposed        | 5 / 51 (9.80%)  |  |  |
| occurrences (all)                  | 7               |  |  |
| 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 | <ul style="list-style-type: none"><li>Clarified guidance to investigators about monitoring participants for hypercalcemia upon discontinuation or interruption of investigational product.</li><li>Added month 60 to the Schedule of Assessments for clarity.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 23 January 2018  | <p>The objective of Study 20140114 was to continue to follow participants with GCTB who were treated in Study 20062004. A minor language of inclusion criterion 101 was updated to clarify that:</p> <ul style="list-style-type: none"><li>To be considered potentially eligible for this study, a participant must have participated in the parent 20062004 study and had completed participation in that study, and</li><li>A participant could not be concurrently enrolled to Study 20062004 and Study 20140114; which was not clear according to the original protocol inclusion criterion 101.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 23 August 2018   | <p>Schedule of Activities</p> <ul style="list-style-type: none"><li>Changed the interval between last dose of denosumab and the EOT in person clinic visit.</li></ul> <p>Study Treatments</p> <ul style="list-style-type: none"><li>Added detail to denosumab dosing instructions.</li></ul> <p>Serious Adverse Events</p> <ul style="list-style-type: none"><li>Clarified procedure for reporting serious adverse events and/or events of interest for participants who experienced a treatment gap of more than 30 days between the EOS visit of Study 20062004 and signing the ICF for Study 20140114.</li></ul> <p>Study Rationale</p> <ul style="list-style-type: none"><li>Clarified that Study 20062004 ended in May 2018, as the study was extended by a year.</li><li>Clarified that participants with surgically salvageable disease, treatment continued until surgery for complete resection and for approximately 6 months after surgery, as aligned to the 20062004 study.</li></ul> <p>Overall Design</p> <ul style="list-style-type: none"><li>Clarified that the EOS visit for all participants was at 5 years. Cohort A participants 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.</li></ul> <p>Lost to Follow-up</p> <ul style="list-style-type: none"><li>Clarified that investigators will not search publicly available records to ascertain survival status when a participant is lost to follow-up.</li></ul> <p>Discontinuation of Study Treatment</p> <ul style="list-style-type: none"><li>Clarified that upon discontinuation, participant's risk for vertebral fragility fractures were evaluated. This language was being added to align language with the core data sheet.</li></ul> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported