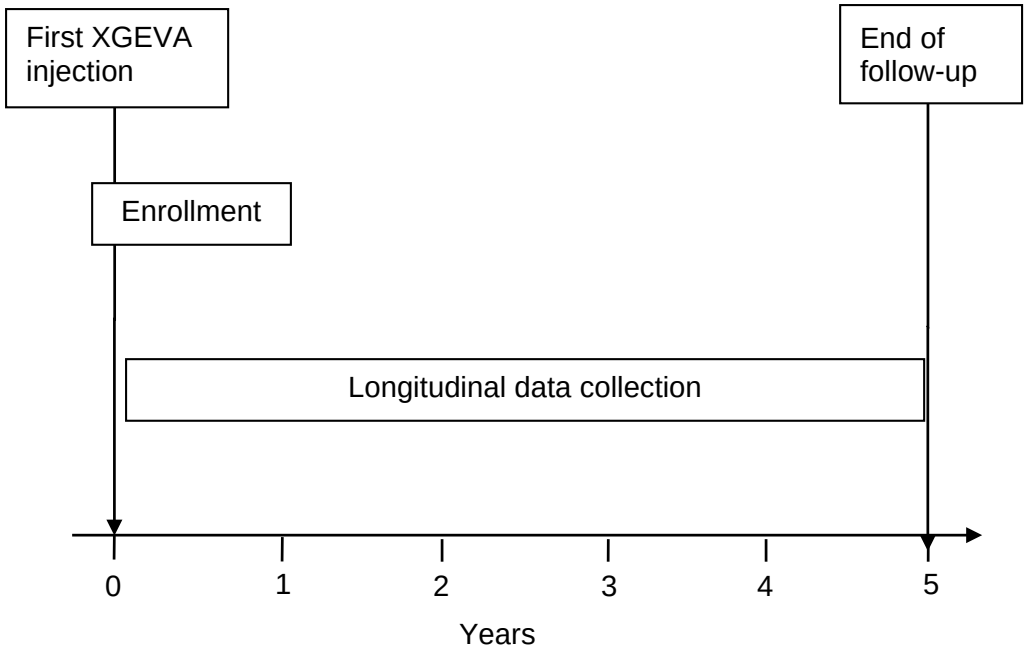
Summary Table of Study Protocol

Title	Prospective Observational Non-interventional Study to Describe Characteristics and Management of Patients With Giant Cell Tumor of Bone Treated With XGEVA and Its Use in Routine Clinical Practice in France
Protocol version identifier	*Version 1.0*
Date of last version of the protocol	18 May 2017
EU Post Authorisation Study (PAS) Register No	NA
Active Substance	Denosumab
Medicinal Product	XGEVA
Product Reference	EU/1/11/703/001 EU/1/11/703/002
Procedure Number	NA
Marketing Authorisation Holder(s)	Amgen
Joint PASS	NA
Research Question and Objectives	Primary objective: To describe patient and disease characteristics of Giant Cell Tumor of Bone (GCTB) patients prior to initiation of XGEVA
Country(-ies) of Study	France
Author	[redacted]

Marketing Authorisation Holder

Marketing authorisation holder(s)	Amgen Europe B.V. Minervum 7061 4817 ZK Breda The Netherlands
MAH Contact	N/A

Study Design Schema



3. Responsible Parties

Scientific committee

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4. Abstract

- Study Title

Prospective Observational Non-Interventional Study to Describe Characteristics and Management of Patients With Giant Cell Tumor of Bone Treated With XGEVA and Its Use in Routine Clinical Practice in France

- Study Background and Rationale

The French Health Authorities requested, in July 2015, a study with the objective to provide long-term data on patients with giant cell tumour of bone treated with XGEVA". This study should be able to provide real world data on the characteristics of treated patients, the conditions of use of XGEVA, the XGEVA impact on morbidity and the Health related quality of life of the patients.

- Research Question and Objective(s)
  - Primary Objective(s)
    To describe patient and disease characteristics of giant cell tumor of bone (GCTB) patients prior to initiation of XGEVA
  - Secondary Objective(s)
    - To describe treatment history and line of treatment prior XGEVA initiation
    - To describe the proportion of patients with GCTB who had surgery at one year from XGEVA initiation, applicable only to the potentially operable patients.
    - To describe treatment patterns, in terms of dosage, frequency of injections, duration of treatment, discontinuation including reason, number of reintroductions of XGEVA, and other specific therapies targeting GCTB (including chemotherapy, bisphosphonates, surgery, radiation, others) administered during the study period

- To evaluate time to tumor progression (TTP) from XGEVA initiation
- To evaluate progression-free survival (PFS) from XGEVA initiation
- To evaluate reccurence free survival after surgery, in patients who had surgery at one year
- To assess pain and impact of pain on health-related quality of life (HRQoL) scores using the Brief Pain Inventory - Short Form (BPI-SF) by dimension
- To assess time to BPI-SF score deterioration from XGEVA initiation
- To describe adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs) possibly related to XGEVA treatment, in particular osteonecrosis of the jaw (ONJ), as collected in routine clinical practice

– Hypothesis(es)/Estimation
This study is generally descriptive in nature, no hypothesis will be carried out.

- Study Design/Type

This is a multicenter, observational non-interventional, prospective study in GCTB patients receiving XGEVA using the French Sarcoma Network.

- Study Population or Data Resource

The French Sarcoma Network is a clinical and pathological network relying on approximately 20 reference centers specialized in sarcoma and rare bone tumours management. Among them, 13 perform the histopathological assessment of GCTB diagnosis. All submitted cases are recorded in a centralized database and completed with clinical recommendation on the management. Potential eligible GCTB patients will be selected through this database.

- Summary of Subject Eligibility Criteria
  - Inclusion Criteria: Adults (aged > 18 years) and skeletally mature adolescents with GCTB initiating a treatment with denosumab (XGEVA) as per respective EU summary of product characteristics (SmPC).
  - Exclusion Criteria: Prior treatment with denosumab (XGEVA or Prolia®).
- Follow-up

The individual follow-up period will be 5 years from XGEVA initiation, whether XGEVA is discontinued or not during the study period, to be able to assess treatment duration and capture retreatment with XGEVA if any.

As part of this observational study follow-up visits are planned at 1 month after XGEVA initiation and then approximately every 3 months, according to the clinical routine practice of the center. If the subject discontinues XGEVA during the study period, the follow-up visits will be every 6 months.

The BPI-SF will be provided to the subject at each follow-up visit as part of the observational study. At enrollment, the BPI-SF should be completed by the subject before the first XGEVA injection. Moreover, in the case of surgery, the BPI-SF shall be handed out to the subject before surgery and at hospital discharge in order to capture change of BPI-SF in post-surgery phase (potential response shift).

- Variables
  - *Outcome Variable(s)*
    - Demographics, clinical and radiological disease characteristics prior to initiation of XGEVA,
    - Line of treatment at XGEVA initiation, defined as permanently inoperable or potentially operable,
    - Proportion of patients undergoing surgery within one year from XGEVA initiation, the estimation will be based on the subgroup of patients defined as potentially operable,
    - Treatment patterns of XGEVA and other treatments targeting GCTB, including type of surgery, radiation and others, administered over the study period (even after XGEVA discontinuation during the planned study period),
    - Time to tumor progression (TTP), defined as the time elapsed between XGEVA initiation and tumor progression,
    - Progression-free survival (PFS), defined as the time elapsed between XGEVA initiation and tumor progression or death from any cause, whichever occurs first,
    - Reccurence free survival, defined as the time elapsed between date of surgery and date of the first recurrence or death from any cause, whichever occurs first,
    - Pain score and impact of pain on patient's lives will be recorded through the BPI-SF which is a patient completed questionnaire that has been shown to be a valid measure of pain in cancer.
    - Time to BPI-SF score deterioration, defined according to Anota et al. (Anota, Hamidou et al. 2015), with a 2 points difference in score as a miniminal clinically important difference,
    - Nature, status and severity of ADRs possibly related to XGEVA treatment will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE, V4),
  - *Other Covariate(s)*
    - Tobacco use
    - Level of qualification
- Study Sample Size

GCTB is a rare bone tumor with an estimated 100 incident cases annualy in France. Some of these patients present a salvageable tumor requiring limited surgical resection

and no denosumab. According to expert opinion the XGEVA GCTB target population is around 50 to 60 patients per year, and 25 to 40 patients are expected to be enrolled per year in the study. The inclusion period is planned over a 2 years period. The analysis is intended to be descriptive in nature, and consequently, the sample size is assessed in terms of the expected levels of precison for estimating the mean age of patients prior to initiation of XGEVA. A sample size of approximately 50 to 80 subjects will provide a half-width of the 95% confidence interval (CI) around point estimates of at most 14% and 11% respectively, when assuming a point estimate of 50%, where the 95% CI is the widest.

- Data Analysis

All analyses will be done using modified intent to treat principle: all included subjects who have received at least one dose of XGEVA treatment (mITT1). For the secondary endpoints, data summaries will be presented overall and by subgroup, according to the occurence of surgery at one year, except recurrence free survival that will estimated only in subjects who had surgery at one year.

Categorical outcomes will be summarized by the number and percentage of patients in each category, and the corresponding 95% CI. Continuous data will be described by mean, standard deviation, median, Q1 and Q3 quartiles and minimum and maximum values.

Time to event endpoints will be analysed using Kaplan Meier estimation and described using median or rate at specific time point with a 95% CI. Follow-up will be calculated using reverse Kaplan Meier estimation.

All BPI SF analyses will be perfomed in all included subjects who have received at least one dose of XGEVA and with a BPI SF score at baseline (mITT2). Longitudinal BPI-SF score will be studied using time to event approach (eg, time to BPI SF score deterioration) and also using mixed model analysis of variance for repeated measurement or pattern mixture models (in case of missing not at random BPI SF score). The BPI SF analyses will be repeated after multiple imputation as sensitivity analyses on the mITT1 population.

The impact of clinical characteristics and treatment on progression will be studied as exploratory purpose only with log rank test and Cox analyses.