PASS INFORMATION

Title	Integrated Retrospective Analysis of Metastatic-related and Non-metastatic-related Fractures in Studies 20050136, 20050244, and 20050103
Version Identifier of the Final Study Report	20180024 Final Report version 1.0
Date of Last Version of the Study Report	08 May 2019
EU PAS Register No:	EUPAS24775
Active Substance	Denosumab
Medicinal Product	XGEVA®
Product Reference:	AMG 162
Procedure Number:	Not Applicable
Marketing Authorization Holder	Amgen, Inc.
Joint PASS	Yes
Research Question and Objectives	This study was planned to fulfil a postmarketing commitment to the United States (US) Food and Drug Administration (FDA) (part of the approval of XGEVA® prior approval supplement, which added Multiple Vertebral Fractures [MVF] Following Treatment Discontinuation to Warnings & Precautions section of XGEVA US Prescribing Information). The primary objective was to characterize the on-study metastatic and nonmetastatic fractures seen in Studies 20050136, 20050244, and 20050103 and assess location of nonmetastatic fracture (vertebral vs nonvertebral). The secondary objective was to describe baseline medications known to reduce bone mineral density and/or a history of osteoporosis in those patients experiencing a nonmetastatic fracture
Countries of Study	Not applicable
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1. ABSTRACT

- **Title**

Integrated Retrospective Analysis of Metastatic-related and Non-metastatic-related Fractures in Studies 20050136, 20050244, and 20050103

- **Keywords**

bone metastases; denosumab; metastatic fracture; vertebral fracture; XGEVA

- **Rationale and Background**

The United States (US) Food and Drug Administration (FDA) approved a safety update to add "Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation" to the XGEVA US Prescribing Information Warning and Precautions section. As the FDA were unable to observe multiple vertebral fractures after treatment discontinuation in patients with solid tumors, the FDA wanted to ensure that safety and efficacy were maintained during the active treatment period, and evaluate whether XGEVA was detrimental to bone for nonmetastatic fractures. As part of this postapproval commitment to the FDA, Amgen performed a retrospective analysis of the active treatment periods of Studies 20050136, 20050244, and 20050103 in subjects with bone metastases from solid tumors to characterize the nonmetastatic fractures.

- **Research Question and Objectives**

Primary: To characterize the on-study metastatic and nonmetastatic fractures seen in the 3 studies (20050136, 20050244, and 20050103) and assess location of nonmetastatic fracture (vertebral vs nonvertebral).

Secondary: To describe baseline medications known to reduce bone mineral density (BMD) and/or a history of osteoporosis in those patients experiencing a nonmetastatic fracture.

- **Study Design**

Retrospective, Amgen database analysis of double-blind Studies 20050136, 20050244, and 20050103 in subjects with bone metastases from solid tumors.

- **Setting**

Subjects were receiving denosumab 120 mg every 4 weeks (Q4W) or zoledronic acid 4 mg Q4W. The cohort of subjects with multiple myeloma from Study 20050244 was not included in this analysis because of the FDA request to analyze subjects with solid tumors only.

- **Subjects and Study Size, Including Dropouts**

All randomized subjects in the 3 studies (20050136, 20050244, and 20050103, excluding 179 subjects with multiple myeloma in Study 20050244) were included.

- **Variables and Data Sources**

Demographics and baseline characteristics were summarized for the primary analysis set, the pathologic fracture analysis set, and the nonmetastatic fracture analysis set. Event rates of pathologic, metastatic, nonmetastatic, vertebral, and nonvertebral fractures and subject incidences of pathologic, metastatic, nonmetastatic, vertebral,

nonvertebral, multiple vertebral, and single vertebral fractures were determined. Exposure was assessed in terms of the total dose of investigational product and the number of days on study.

- **Results**

Results are summarized in Table 1-1. Results in the text are provided for denosumab and zoledronic acid groups, respectively.

Table 1-1. Summary of Results in Study 20180024

Parameter	Details	Denosumab 120 mg Q4W	Zoledronic Acid 4 mg Q4W
Disposition	N	2776	2768
Baseline characteristics			
Demographics	Men, n (%)	1489 (53.6)	1458 (52.7)
	Women, n (%)	1287 (46.4)	1310 (47.3)
	White, n (%)	2353 (84.8)	2320 (83.8)
	Mean (SD) age, years	62.1 (12.3)	62.6 (12.1)
Disease characteristics	Breast cancer, n (%)	1026 (37.0)	1020 (36.8)
	Prostate cancer, n (%)	950 (34.2)	951 (34.4)
	Previous skeletal-related event, n (%)	1055 (38.0)	1094 (39.5)
	Previous oral bisphosphonate use, n (%)	100 (3.6)	101 (3.6)
	History of osteoporosis, n (%)	174 (6.3)	164 (5.9)
Study outcomes			
Subject incidence[a]			
Pathologic fracture		522 (18.8) (17.4, 20.3)	595 (21.5) (20.0, 23.1)
Metastatic fracture		312 (11.2) (10.1, 12.5)	339 (12.2) (11.0, 13.5)
Nonmetastatic fracture		261 (9.4) (8.3, 10.5)	326 (11.8) (10.6, 13.0)
Nonmetastatic vertebral fracture		109 (3.9) (3.2, 4.7)	162 (5.9) (5.0, 6.8)
Nonmetastatic nonvertebral fracture		178 (6.4) (5.5, 7.4)	188 (6.8) (5.9, 7.8)
Nonmetastatic multiple vertebral fracture		32 (1.2) (0.8, 1.6)	40 (1.4) (1.0, 2.0)
Nonmetastatic single vertebral fracture		77 (2.8) (2.2, 3.5)	122 (4.4) (3.7, 5.2)
Time to first metastatic fracture	Metastatic fracture analysis set Mean (SD), months	6.89 (6.41)	7.56 (6.67)
Months on study	Pathologic fracture analysis set Mean (SD), months	17.8 (9.0)	17.1 (9.0)
Number of active dose received	Pathologic fracture analysis set Mean (SD)	18.1 (9.8)	16.6 (9.5)

N = number of subjects in the primary analysis set; n = number of subjects with the given characteristic; Q4W = every 4 weeks

[a] Data are n (%) (95% CI).

Percentage is based on the number of subjects in the primary analysis set.

- **Discussion**

The results of this retrospective analysis are consistent with the primary and secondary endpoints reported in each clinical study analyzed (Studies 20050103, 20050136, and 20050244). On-treatment multiple vertebral fractures did occur; however, they were infrequent and balanced between treatment groups.

- **Marketing Authorization Holder(s):** Amgen, Inc.
- **Names and Affiliations of Principal Investigators:** Available upon request.