

# **Predictors of clinically meaningful bone mineral density gains with romosozumab: An explainable machine learning analysis of a real-world cohort**

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## **Abstract-**

**Objective**To evaluate the real-world effectiveness of Romosozumab in postmenopausal women with severe osteoporosis and to identify baseline clinical and biochemical predictors of clinically meaningful bone mineral density (BMD) gains ( $\geq 10\%$ , used for exploratory classification) using an explainable machine-learning approach.**Methods**We conducted a retrospective, observational multicentre study across seven hospitals in Castilla-La Mancha, Spain. Postmenopausal women aged  $\geq 50$  years who initiated romosozumab between May 2023 and November 2024 for severe osteoporosis or high fracture risk were included. Lumbar-spine, femoral-neck, and total-hip BMD were assessed by dual-energy X-ray absorptiometry (DXA) at baseline and 12 months. Baseline biochemical variables included serum P1NP, CTX, PTH, vitamin D, calcium, phosphate, alkaline phosphatase, and creatinine. Predictors of a  $\geq 10\%$  BMD gain were examined using elastic-net logistic regression combined with SHapley Additive exPlanations (SHAP) for model interpretability.**Results**Fifty-eight women were analysed (mean  $\pm$  SD age 71.7  $\pm$  10.0 years; BMI 26.1  $\pm$  4.8 kg/m<sup>2</sup>; mean age at menopause 47.3  $\pm$  6.0 years). Mean 12-month BMD increases were +15.35% at the lumbar spine, +12.42% at the femoral neck, and +8.62% at the total hip. The proportion achieving a  $\geq 10\%$  gain was 39%, 38.1%, and 31.7%, respectively. SHAP analysis identified consistent predictors of response: lower baseline BMD, higher phosphate levels, and younger age at menopause were associated with greater gains, whereas elevated PTH and alkaline phosphatase predicted a reduced response. Patients who had not received corticosteroids or NSAIDs in the six months prior to treatment initiation, typically for pain or inflammation, also showed greater increases in BMD.**Conclusions**Romosozumab was effective and well-tolerated in routine clinical practice, yielding meaningful and site-specific gains in BMD. Explainable machine-learning analysis identified physiologically coherent and consistent clinical predictors of  $\geq 10\%$  response.

**Index Terms-** Romosozumab; Osteoporosis; Machine learning; Bone mineral density; Predictors; Real-world evidence

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