

Reply to: A Bisphosphonate With a Low Hydroxyapatite Binding Affinity Prevents Bone Loss in Mice After Ovariectomy and Reverses Rapidly With Treatment Cessation

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To The Editor

We thank Dr Pazianas for his comments emphasizing certain points raised in the discussion and conclusion of our article.¹ There, we had endeavored to point out that this was a proof-of-concept study testing the utility of a rapidly reversible bisphosphonate (NE-58025) in preventing bone loss. The only specific subsequent use for NE-58025 that we endorsed at this very early stage of research was to explore the biomechanical consequences of a drug holiday. This obviously points to a preclinical research study in which such bone biomechanical studies can be performed. We further noted that short-acting bisphosphonates that might require daily treatment could be problematic from a clinical perspective. We regret any confusion that might have resulted from our discussion.

The letter also offers several speculations about negative “off-target” (i.e., outside of bone) effects caused by high circulating levels of low-affinity bisphosphonate compounds, including the potential to develop osteonecrosis of the jaw. Off-target effects are a concern with almost all drugs, and the specific points noted should be investigated in future studies designed to focus on these issues.

Finally, we note a potentially confusing typographical error. The letter refers to both NE-58025 and NE-58024; only one compound (NE-58025) was studied in our research.

Author Contributions

Abigail Coffman: Writing-review & editing. **Jelena Basta-Pljakic:** Writing-review & editing. **Rosa Guerra:** Writing-review & editing. **Frank Ebetino:** Writing-review & editing. **Mark Lundy:** Writing-review & editing. **Robert Majeska:** Writing-review & editing. **Mitchell Schaffler:** Writing-review & editing.

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Reference

1. Coffman AA, Basta-Pljakic J, Guerra RM, et al. JBMR Plus: A bisphosphonate with a low hydroxyapatite binding affinity prevents bone loss in mice after ovariectomy and reverses rapidly with treatment cessation. *JBMR Plus*. 2021;5(4):e10476.

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