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Dosing Strategies of Bone-Targeting Agents—Reply

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In Reply

We appreciate the comments by Hutton et al regarding dosing frequency and the need to examine alternative dosing intervals. Given our study design, which used a single infusion, we do not know whether a different dosing interval would have been more or less effective or generated more or fewer adverse events in this cohort. However, because a single infusion of zoledronic acid has been shown to exert a positive effect on skeletal health for up to 5 years,^{1–2} we chose a 2-year dosing interval. We agree that additional research needs to be done on the dosing frequency, especially focusing on frail elderly patients for whom there are limited data on osteoporosis treatment.

We thank Dr Uzoigwe for asking about the possibility of index event bias.³ He suggests that the lack of fracture reduction in our study may have resulted from inclusion of a high proportion of patients who had previously failed treatment with an analogous therapy. It is worth reemphasizing that our study was neither designed nor powered to assess fracture reduction. Instead, our goal was to determine whether we could discern an effect of bisphosphonate therapy on bone density and turnover. Without such an effect, bisphosphonate therapy would be less likely to reduce fractures.

As to enrolling patients resistant to bisphosphonates, we believe this is unlikely to have occurred for 2 reasons. First, although we do not know precisely how many of our participants received a bisphosphonate in the past, the number is likely low. Our exclusion criteria, based on detailed record review for the 2 years prior to enrollment, helped ensure this. More remote information was limited by the high prevalence of cognitive impairment among our participants and our limited access to their medical records prior to their moving to the facility. Our unpublished pilot data from 2007, drawn from the same sites, revealed that only 3.6% of residents were taking a bisphosphonate, an even lower rate than the 5.5% to 19% reported in other states.^{4–5} The low usage is not surprising given the logistical difficulty of administering these agents in a nursing home setting. In addition, although 46% of our subjects had a previous radiographic vertebral fracture,⁶ and an additional 4% had a prior hip or other fracture, our patients and physicians were aware of such a fracture in only 20% of cases. If considered at all, bisphosphonate therapy would likely have been

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considered only for these 20%. The second aspect of index event bias relates to inclusion of patients with proven resistance to a related drug. Owing to the high prevalence of bisphosphonate adverse effects—especially given the use of predominantly oral agents during the period of our study—it seems more likely that, among the small number of subjects who may have previously used a bisphosphonate, the decision to discontinue it would be based on adverse effects rather than failure to prevent a fracture. Thus, we believe that index bias is unlikely to have had a significant effect on our results.

References

1. Reid IR, Black DM, Eastell R, et al. HORIZON Pivotal Fracture Trial and HORIZON Recurrent Fracture Trial Steering Committees. Reduction in the risk of clinical fractures after a single dose of zoledronic Acid 5 milligrams. *J Clin Endocrinol Metab.* 2013; 98(2):557–563. [PubMed: 23293335]
2. Grey A, Bolland MJ, Horne A, et al. Five years of anti-resorptive activity after a single dose of zoledronate--results from a randomized double-blind placebo-controlled trial. *Bone.* 2012; 50(6): 1389–1393. [PubMed: 22465268]
3. Dahabreh IJ, Kent DM. Index event bias as an explanation for the paradoxes of recurrence risk research. *JAMA.* 2011; 305(8):822–823. [PubMed: 21343582]
4. Colón-Emeric C, Lyles KW, Levine DA, et al. Prevalence and predictors of osteoporosis treatment in nursing home residents with known osteoporosis or recent fracture. *Osteoporos Int.* 2007; 18(4): 553–559. [PubMed: 17120179]
5. Parikh S, Brookhart MA, Stedman M, Avorn J, Mogun H, Solomon DH. Correlations of nursing home characteristics with prescription of osteoporosis medications. *Bone.* 2011; 48(5):1164–1168. [PubMed: 21320653]
6. Greenspan SL, Perera S, Nace D, et al. FRAX or fiction: determining optimal screening strategies for treatment of osteoporosis in residents in long-term care facilities. *J Am Geriatr Soc.* 2012; 60(4): 684–690. [PubMed: 22316237]