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Monte Carlo Resampling Validates Use of Bone Mineral Density as Surrogate to Replace Fracture in Future Randomized Trials of Osteoporosis Treatments: Results From SABRE

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Context: Despite effective osteoporosis therapies, many high-risk patients remain untreated. Furthermore, no new treatments are in advanced stage development. To enable more patient/physician choices, we aimed to create a new pathway for the development of osteoporosis treatments. Thus, we initiated the Study to Advance BMD as a Regulatory Endpoint (SABRE) to assess whether trial fracture endpoints could be replaced by a surrogate of 2-year treatment-related change in total hip BMD (ΔBMD%). We collected individual patient data (IPD) from >50 trials of

osteoporosis drugs, including >150,000 patients. Using this database, we established the surrogate threshold effect (STE), defined as the ΔBMD% that would be predicted to reduce fracture risk significantly. We computed the STE for five fracture outcomes [vertebral (1.43%), hip (3.07%), non-vertebral (2.13%), all (1.83%), and all clinical (2.04%)].

Objective: To assess the performance of the STE for theoretical osteoporosis treatment trials designed using BMD as a primary endpoint.

Methods: We used IPD from trials in the SABRE database, which had at least 500 participants in the active and placebo treatment arms with 2-year BMD measurements. Eleven studies (59,000 patients) met the criteria for inclusion in this analysis. Monte Carlo resampling with replacement was used within each study to generate 1,000 trials of total sample sizes (n = 100, 250, 500, 750, 1,000). The mean and 95% lower confidence limit of the mean estimate (LCL) of treatment-related ΔBMD% was then compared to the STE in each of the 1,000 replications. The proportion of trials in which the ΔBMD%-STE comparison was concordant with the fracture reduction in the whole trial was computed for each trial and fracture outcome.

Results: The concordance between the ΔBMD%-STE comparison and the fracture reductions increased with larger sample sizes reaching a plateau at n = 500. Among 37 study and fracture combinations assessed, 34 (92%) had concordant results between the mean ΔBMD%-STE comparison and observed fracture risk reduction. Comparing the LCL of ΔBMD% estimates to the STE resulted in similar concordance at large sample sizes (≥500).

Conclusion: Our results support treatment-related total hip BMD % change as a surrogate endpoint for fracture in future osteoporosis trials. These results suggest that future studies using BMD as a primary endpoint should include at least 500 patients with BMD measurement at 2 years. Compared to fracture endpoint trials, this smaller and shorter study design will decrease drug development costs and prompt innovation in osteoporosis drug development, ultimately resulting in more choices for patients and physicians.

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