

# **Ibandronate Reduces Clinical and Nonvertebral Fracture Risk in Women Postmenopausal Osteoporosis (PMO): Results of Pooled Analysis of Clinical Trials**

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**BACKGROUND:** Data from the 4 pivotal phase III clinical trials of ibandronate (IBN) were pooled and analyzed to assess fracture efficacy of IBN at increasing doses and levels of annual cumulative exposure (ACE) in women with PMO.

**METHODS:** This pooled analysis included all patients in the intent-to-treat (ITT) population who received oral or IV doses of IBN or placebo (PBO) in 4 studies (IV dose fracture study, BONE, MOBILE, and DIVA). BONE and the IV dose fracture study were 3-year fracture trials versus PBO. MOBILE and DIVA were 2-year BMD active-controlled studies that examined fractures as secondary endpoints. Doses were grouped by ACE, ie, high ( $\geq 10.8$ mg includes 150mg oral monthly, 3mg IV quarterly, and 2mg every 2 months [q2mo]), mid (5.5-7.2mg), and low ( $\leq 4.0$ mg) annual doses. ACE was computed by multiplying the drug strength (mg) by the number of annual doses and an absorption factor (0.6% for oral and 100% for IV). Cox hazards models, which controlled for age, baseline BMD T-score, and clinical fracture history, were used to estimate fracture risk with IBN vs PBO. The analysis was not stratified by study due to confounding with ACE. Fracture groups examined included all clinical fractures (both vertebral and nonvertebral), nonvertebral fractures (NVFs), and a subgroup of the 6 major NVFs (clavicle, humerus, wrist, pelvis, hip, leg). Log-rank tests were used to compare time-to-fracture for different ACE groups.

**RESULTS:** In this pooled analysis, 1924 patients received PBO, 1911 received 2.0- $<$ 4.0mg ACE, 3585 received 5.5-7.2mg ACE, and 1290 received  $>$ 10.8mg ACE. The group that received the highest annual doses of IBN ( $>$ 10.8 mg) had a reduction in relative risk of 28.8% for all clinical fractures, 29.9% for NVFs, and 34.4% for the subgroup of 6 NVFs compared with PBO (Table). Based on log-rank test, the high ACE group demonstrated a greater time-to-fracture vs PBO for all clinical fractures ( $P=0.002$ ), and NVFs ( $P=0.025$ ) at 2 years.

**CONCLUSION:** In this pooled analysis, it was observed that doses of ibandronate resulting in ACEs of  $>$ 10.8mg—which includes the marketed doses of 150mg monthly oral and 3mg IV quarterly—significantly reduce the risk of clinical fractures and NVFs.

Table. Adjusted hazard ratios for fractures at varying dose levels relative to placebo (ITT)				
Fracture type (ACE in mg)	Adjusted hazard ratio	95% CI	P value	
<b>All clinical</b> (vertebral + nonvertebral)				
High* ( $\geq 10.8$ )	0.712	0.55–0.92	0.010 <sup>†</sup>	
Mid <sup>‡</sup> (between 5.5 and 7.2)	0.881	0.74–1.05	0.148	
Low <sup>§</sup> ( $\leq 4.0$ )	0.887	0.73–1.07	0.211	
<b>Nonvertebral</b> (all sites)				
High* ( $\geq 10.8$ )	0.701	0.50–0.99	0.041 <sup>†</sup>	
Mid <sup>‡</sup> (between 5.5 and 7.2)	1.04	0.83–1.30	0.722	
Low <sup>§</sup> ( $\leq 4.0$ )	0.893	0.69–1.15	0.383	
<b>Key nonvertebral sites</b> (clavicle, humerus, wrist, pelvis, hip, and leg)				
High* ( $\geq 10.8$ )	0.656	0.45–0.96	0.032 <sup>†</sup>	
Mid <sup>‡</sup> (between 5.5 and 7.2)	1.15	0.90–1.46	0.270	
Low <sup>§</sup> ( $\leq 4.0$ )	0.871	0.66–1.15	0.334	
*includes 150mg oral monthly, 3mg IV quarterly, and 2mg IV q2mo; <sup>†</sup> Significance defined as $P < 0.05$ (unadjusted for multiple comparisons); <sup>‡</sup> include 2.5mg daily oral, 20mg oral intermittent, 2 x 50mg monthly oral, 100mg monthly oral; <sup>§</sup> includes 0.5mg IV q3mo and 1.0mg IV q3mo; ACE, annual cumulative exposure				