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## Review

Update on long-term treatment with bisphosphonates for postmenopausal osteoporosis: A systematic review<sup>☆</sup>Q1 Erik F. Eriksen<sup>a,\*</sup>, Adolfo Díez-Pérez<sup>b</sup>, Steven Boonen<sup>c,1</sup><sup>a</sup> Department of Endocrinology, Oslo University Hospital, Oslo, Norway<sup>b</sup> Department of Internal Medicine, Hospital del Mar, IMIM—Autonomous University of Barcelona and RETICEF, Barcelona, Spain<sup>c</sup> Department of Geriatrics, Leuven University Hospital, Leuven, Belgium

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## ABSTRACT

**Introduction:** Osteoporosis is a progressive skeletal disorder that requires long-term treatment. However, there is little guidance regarding optimal treatment duration and what the treatment discontinuation and retreatment criteria should be. Given that bisphosphonates are the most commonly prescribed class of agent for the treatment of osteoporosis, we reviewed the long-term data relating to these therapies and discussed the considerations for using bisphosphonates in postmenopausal women with osteoporosis.

**Methods:** A PubMed search, using the search terms 'bisphosphonate', 'postmenopausal osteoporosis' and 'long term' and/or 'extension' was conducted in January 2013. Results from 9 controlled studies that prospectively assessed alendronate, risedronate, ibandronate or zoledronic acid in women with postmenopausal osteoporosis were reviewed.

**Findings:** Clinical studies in postmenopausal women with osteoporosis showed that long-term use of bisphosphonates resulted in persistent anti-fracture and bone mineral density (BMD) increasing effects beyond 3 years of treatment. No unexpected adverse events were identified in these studies and the long-term tolerability profiles of bisphosphonates remain favorable. Data from the withdrawal extension studies of alendronate and zoledronic acid also showed that residual fracture benefits were seen in patients who discontinued treatment for 3 to 5 years after an initial 3- to 5-year treatment period. BMD monitoring and fracture risk assessments should be conducted regularly to determine whether treatment could be stopped or should be reinitiated. Patients exhibiting T-scores < -2.5 or who have suffered a new fracture while on treatment should continue treatment, while patients with T-scores > -2.5 could be considered for discontinuation of active treatment while undergoing continued monitoring of their bone health. The duration and potential discontinuation of treatment should be personalized for individual patients based on their response to treatment, fracture risk and comorbidities.

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\* Corresponding author at: Department of Endocrinology, Oslo University Hospital, Pb 49596 Nydalen, N-0424 Oslo, Norway.

E-mail address: [e.f.eriksen@medisin.uio.no](mailto:e.f.eriksen@medisin.uio.no) (E.F. Eriksen).

<sup>1</sup> Deceased.

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69

## 70 Introduction

71 Osteoporosis is the most common bone disease in humans and  
 72 affects both men and women [1]. It is a progressive skeletal disorder  
 73 characterized by low bone mass and structural deterioration of bone  
 74 tissue, leading to bone fragility and an increased risk of fracture [2]. In  
 75 particular, hip fractures constitute the most serious of all osteoporotic  
 76 fractures; they are associated with increased morbidity and mortality,  
 77 and decreased ambulation, and are responsible for direct and indirect  
 78 lifetime costs in excess of \$20 billion in the United States of America  
 79 (estimated cost in 1997) [3], and over £2 billion in the United Kingdom  
 80 (in 2012) [4]. The burden of osteoporotic hip fractures increases with  
 81 age. In the recently published Global Longitudinal study of Osteoporosis  
 82 in Women, the proportion of incident hip fractures among incident  
 83 major fractures increased more than five-fold with age, from 6.6%  
 84 among women 55 to 59 years of age to 34% among those  $\geq 85$  years of  
 85 age [5,6].

86 Current pharmacologic therapies for osteoporosis aim to prevent  
 87 fractures through inhibition of bone resorption as well as stimulation  
 88 of formation [7]. Although all the licensed therapies have demonstrated  
 89 fracture risk reduction and/or increased bone mineral density (BMD) in  
 90 clinical trials of postmenopausal osteoporosis, these studies were often  
 91 no longer than 3 to 4 years in duration [8–12]. Owing to the chronic  
 92 nature of osteoporosis and the fact that the burden of fracture increases  
 93 with age, long-term fracture prevention is needed and treatment  
 94 beyond 3 years may be required for the majority of patients.

95 Using anti-osteoporotic therapies for long-term treatment neces-  
 96 sitates a number of considerations such as: Do all patients require  
 97 long-term treatment? Which patients benefit most from long-term  
 98 therapy? What is the long-term efficacy of licensed therapies? Who  
 99 may discontinue treatment and what should the retreatment criteria  
 100 be? Are there any potential safety concerns with chronic use of these  
 101 agents?

102 A recent review by the European Society for Clinical and Economic  
 103 Aspects of Osteoporosis and Osteoarthritis and the International  
 104 Osteoporosis Foundation summarized the long-term fracture efficacy  
 105 and safety data of currently available anti-osteoporotic agents [13],  
 106 but new data have emerged since its publication. Given that bisphos-  
 107 phonates are one of the most commonly prescribed classes of agent  
 108 for osteoporosis [14,15], this article reviews the latest long-term data  
 109 relating to bisphosphonate therapy for the management of osteo-  
 110 porosis, and discusses the results in light of the aforementioned  
 111 considerations for long-term use. The data presented pertain to the  
 112 use of bisphosphonates in women, as no comparable data are available  
 113 for men.

## 114 Methods

115 A PubMed search using the search terms ‘bisphosphonate’,  
 116 ‘postmenopausal osteoporosis’, and ‘long term’ or ‘extension’ was  
 117 conducted in January 2013. The search results were restricted to clinical  
 118 trials only with no time limit. A total of 107 articles were retrieved from  
 119 the search. Only controlled studies that prospectively assessed the use  
 120 of alendronate, risedronate, ibandronate or zoledronic acid in women  
 121 with postmenopausal osteoporosis are included in this review. Studies  
 122 with a duration of  $\leq 3$  years, those that had bone histology or drug  
 123 adherence as the main study end points, and those which involved

<100 patients, assessed conditions other than postmenopausal osteo-  
 porosis, or focused on the use of non-bisphosphonates are excluded.  
 Thus, data from 9 primary articles are reviewed in this paper. No formal  
 meta-analysis of the retrieved articles was carried out because of the  
 heterogeneity of the populations, interventions, lengths of follow up  
 and drugs tested in the trials.

## Long-term efficacy and safety of bisphosphonates

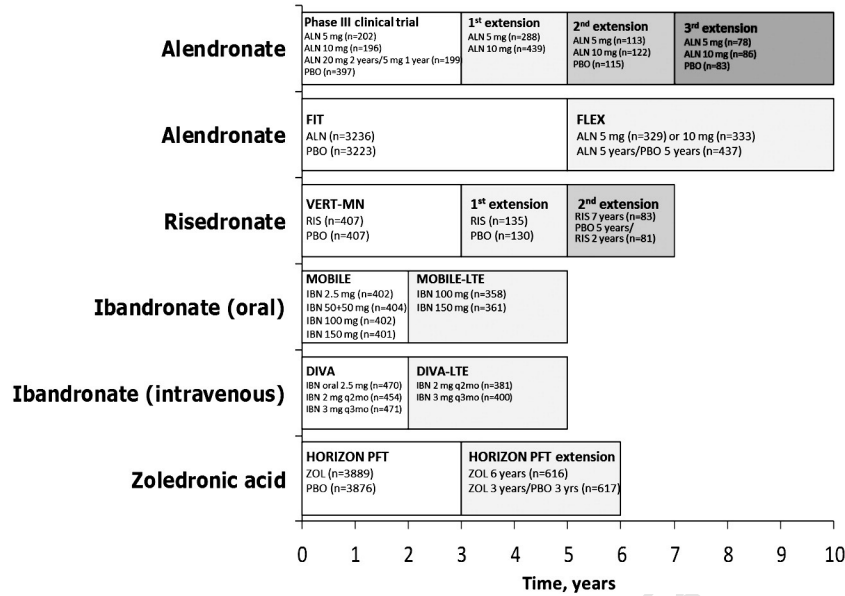
### Long-term efficacy of bisphosphonates

132 Bisphosphonates are antiresorptive agents that decrease bone  
 133 turnover by inhibiting osteoclast function. They are commonly used  
 134 for the prevention or treatment of osteoporosis in women and, in  
 135 some cases, in men. The bisphosphonate therapies currently licensed  
 136 to treat postmenopausal osteoporosis include alendronate, risedronate,  
 137 ibandronate and zoledronic acid. These drugs exhibit different degrees  
 138 of potency for inhibition of the key enzyme in the mevalonate  
 139 pathway, farnesyl phosphate phosphatase, and different affinities for  
 140 hydroxyapatite binding sites on bony surfaces [16]. Bisphosphonates  
 141 are available as oral formulations (alendronate, risedronate and  
 142 ibandronate) for daily, weekly or monthly dosing, or as intravenous  
 143 formulations for bimonthly or quarterly (ibandronate) or yearly  
 144 (zoledronic acid) administration. These characteristics may contribute  
 145 to differences in drug metabolism, compliance and, subsequently, risk  
 146 reduction estimates among the bisphosphonates that are currently  
 147 available [17–23]. However, no prospective head-to-head studies have  
 148 been conducted to assess whether these differences are reflected in  
 149 real life variations among drugs in efficacy or safety.

150 Bisphosphonates have been studied in clinical trials of at least  
 151 3 years in duration with fractures assessed as the primary end point  
 152 [8,9,12,24–27]. The registration trials of alendronate, risedronate and  
 153 zoledronic acid were subsequently extended to investigate the long-  
 154 term effects of these drugs (Fig. 1) [6,28–30]. Long-term studies of  
 155 ibandronate were also carried out but these were performed as  
 156 extensions of the non-placebo-controlled, non-inferiority studies that  
 157 assessed either oral or intravenous ibandronate dosing regimens  
 158 [31–34]. Owing to the size of these extension studies, BMD was assessed  
 159 as the primary outcome measure with fractures often assessed as  
 160 exploratory endpoints or as adverse events.

### Fracture risk reduction with long-term bisphosphonate treatment

161 *Alendronate.* The 5-year, randomized, double-blind Fracture Intervention  
 162 Trial (FIT) Long-term Extension (FLEX) study of alendronate included  
 163 postmenopausal women with osteoporosis who had received an average  
 164 of 5 years of alendronate therapy during and after FIT [28]. The FLEX  
 165 study compared the effect of approximately 10 years of continuous  
 166 alendronate treatment ( $n = 662$ ; mean age, 72.7–72.9 years) with  
 167 cessation of therapy ( $n = 437$ ; mean age, 73.7 years) after 5 years of  
 168 initial treatment. Fracture incidence was assessed as an exploratory  
 169 endpoint and was based on adverse event reporting. The study found a  
 170 significantly lower risk of clinical vertebral fracture among those who  
 171 continued (pooled results of the 5 and 10 mg arms) versus those who  
 172 stopped alendronate treatment (2.4% vs. 5.3%; relative risk, 0.45; 95%  
 173 confidence interval [CI], 0.24–0.85; Fig. 2). However, discontinuation  
 174 did not appear to increase the risk of nonvertebral or morphometric  
 175



**Fig. 1.** Published long-term studies of bisphosphonates for osteoporosis [6,8,9,12,24–34,37]. ALN, alendronate; DIVA, Dosing IntraVenous Administration; FIT, Fracture Intervention Trial; FLEX, Fracture intervention trial Long-term Extension; HORIZON PFT, Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly Pivotal Fracture Trial; IBN, ibandronate; LTE, long-term extension; MOBILE, Monthly Oral IBandronate in LadiEs; PBO, placebo; RIS, risedronate; VERT-MN, Vertebral Efficacy with Risedronate Therapy Multinational; ZOL, zoledronic acid.

176 vertebral fractures during the 5 years of the extension study. Similar  
 177 residual efficacy was reported in the extensions to two 3-year, phase III  
 178 clinical studies in postmenopausal women [35,36]. These two core  
 179 studies, the results of which were combined into one report [37], were  
 180 both randomized, double-blind, placebo-controlled trials with identical  
 181 study designs. A number of who patients enrolled in these trials  
 182 ultimately received alendronate continuously for up to 10 years [35].  
 183 The fact that the incidence of morphometric vertebral and nonvertebral  
 184 fractures did not appear to increase in alendronate-treated patients  
 185 who had experienced 10 years of reductions in bone turnover (80–90%  
 186 suppression) refutes the notion—reported in a small number of  
 187 patients—that bone quality is impaired by long-term antiresorptive  
 188 treatment [38,39].

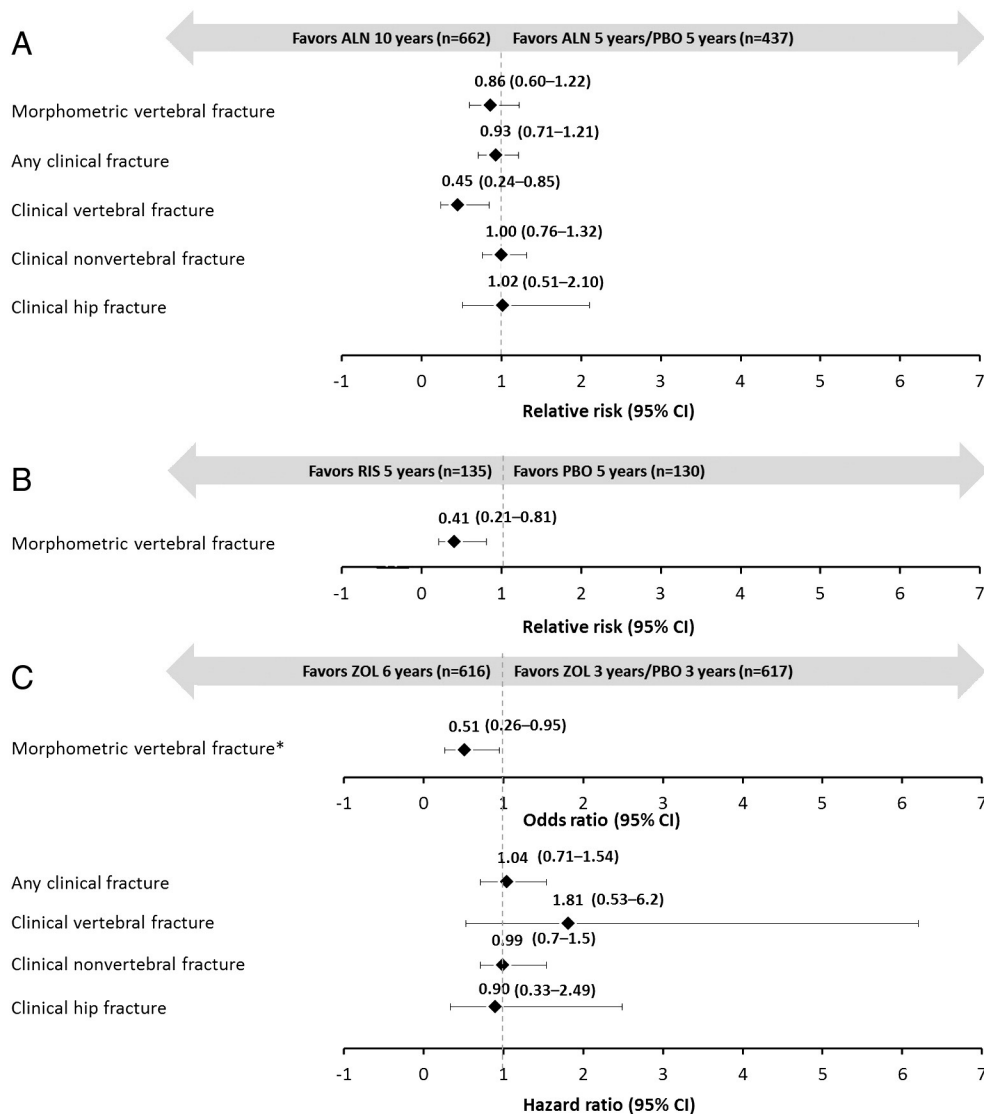
189 A *post hoc* analysis of the FLEX study was carried out to identify  
 190 specific subgroups of patients who may benefit from continued  
 191 alendronate treatment [40]. The analysis found that among women  
 192 with no vertebral fractures but with femoral neck BMD T-score ≤  
 193 −2.5, continued alendronate treatment significantly reduced the risk  
 194 of nonvertebral fractures (relative risk, 0.50; 95% CI, 0.26–0.96). For  
 195 women with a baseline vertebral fracture, however, no significant  
 196 interactions between baseline femoral neck BMD and the effect of  
 197 continued alendronate treatment were observed on any fracture  
 198 outcomes. This analysis was based on a small number of fractures and  
 199 may have limited statistical power.

200 **Risedronate.** Risedronate has also been examined in long-term studies  
 201 of up to 7 years. In the first extension study of the 3-year Vertebral  
 202 Efficacy with Risedronate Therapy Multinational (VERT-MN) trial, 265  
 203 postmenopausal women who had participated in the core study  
 204 continued their original VERT-MN randomization regimen of risedronate  
 205 5mg/day (n = 135; mean age, 72.4years) or placebo (n = 130; mean age,  
 206 72.6 years) for 2 additional years [6]. Compared with placebo,  
 207 risedronate was associated with a 59% reduction in the relative risk of  
 208 radiographic vertebral fracture (95% CI, 19%–79%) between years 4 and  
 209 5 of treatment (p = 0.01; Fig. 2); the magnitude of this reduction was  
 210 consistent with that observed in the first 3 years of risedronate treatment  
 211 in VERT-MN (relative risk reduction, 49%; 95% CI, 27%–64%), suggesting  
 212 a persistent effect over time [12]. Nonvertebral fractures were also

213 reported less frequently among patients receiving risedronate, compared  
 214 with placebo, but the number of fractures was too small to show  
 215 statistical significance. The VERT-MN extension study was continued  
 216 for a further 2 years in which 81 and 83 patients who had received  
 217 placebo and risedronate for 5 years, respectively, received risedronate  
 218 in an open-label fashion [30]. This second extension trial reported a  
 219 decrease in the incidence of radiographic vertebral fracture in the  
 220 placebo/risedronate group in years 6 to 7 (6.2%) compared with years  
 221 0 to 5 (7.6%–12.3%). It should be noted, however, that the numbers of  
 222 patients in these extension studies were small and the patients included  
 223 may not be representative of the VERT-MN core study population.

224 **Ibandronate.** In the long-term studies of ibandronate, fractures were not  
 225 analyzed as a study endpoint but were reported as adverse events. The  
 226 3-year double-blind extension to the 2-year Monthly Oral IBandronate  
 227 in LadiEs (MOBILE) study reported clinical osteoporotic fractures in  
 228 10.3% and 9.1% of patients receiving ibandronate 100 mg (n = 348)  
 229 and 150 mg (n = 350), respectively (mean age of the extension study  
 230 population, 67.6 years) [33]. The respective figures in the MOBILE core  
 231 study were 6.1% (24/396) and 6.8% (27/396) [34]. Similarly, for  
 232 intravenous ibandronate, the 3-year, open-label Dosing IntraVenous  
 233 Administration (DIVA) long-term extension study (DIVA-LTE) reported  
 234 clinical fracture rates of 11.0% in postmenopausal women with  
 235 osteoporosis who received ibandronate 2 mg bimonthly (n = 381;  
 236 mean age, 66.1 years) and 8.5% in those who received ibandronate  
 237 3 mg quarterly (n = 400; mean age, 65.9 years) for a total of 5 years  
 238 [31]. The respective values for the 2-year DIVA core study were 4.7%  
 239 and 4.9% [32]. The fracture rates in both the MOBILE long-term  
 240 extension (MOBILE-LTE) and DIVA-LTE appeared to be higher than in  
 241 the MOBILE and DIVA core studies. However, the study populations  
 242 differed between the core and extension studies due to attrition and  
 243 aging; this, together with the fact that there were no placebo arms in  
 244 these studies, means that few conclusions can be drawn from these  
 245 results.

246 **Zoledronic acid.** The 3-year extension of the Health Outcomes and  
 247 Reduced Incidence with Zoledronic acid ONce yearly Pivotal Fracture  
 248 Trial (HORIZON PFT) adopted a study design that was similar to that



**Fig. 2.** Fracture risks in long-term studies of bisphosphonates for osteoporosis [6,28,29]. A) Relative risk of fracture in patients in the FLEX study; the ALN 10 year results represent pooled data from patients who received alendronate 5 or 10 mg for 10 years; B) Relative risk of fracture in patients in the first extension of the VERT-MN study in which patients received RIS or PBO for 5 years; C) Hazard ratios in the HORIZON PFT extension study. \*Morphometric vertebral fracture assessment was performed in 486 patients who received ZOL for 3 years followed by PBO for 3 years, and in 469 patients who received ZOL for 6 years. ALN, alendronate; CI, confidence interval; FLEX, Fracture intervention trial Long-term Extension; HORIZON PFT, Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly Pivotal Fracture Trial; PBO, placebo; RIS, risedronate; VERT-MN, Vertebral Efficacy with Risedronate Therapy Multinational; ZOL, zoledronic acid.

of the FLEX study [29], albeit of shorter duration (6 years in total). Postmenopausal women with osteoporosis (mean age, 75.5 years) who received zoledronic acid 5 mg during the 3-year HORIZON PFT were randomly assigned to receive zoledronic acid (n = 616) or placebo (n = 617) for 3 additional years in a blinded fashion. As in FLEX, fractures were assessed as part of an exploratory analysis. Zoledronic acid treatment for 6 years was associated with significantly lower risk of morphometric vertebral fractures (odds ratio, 0.51; 95% CI, 0.26–0.95; p = 0.035; Fig. 2) than treatment discontinuation after 3 years [29]. No statistically significant between-group differences were seen with all clinical, clinical vertebral, nonvertebral or hip fractures, but the confidence intervals were wide and do not exclude potential benefits. It is interesting to note that the incidence of morphometric vertebral, nonvertebral and hip fractures in the treatment discontinuation group remained below that in placebo group in the HORIZON PFT. This suggests that there may be substantial residual benefits after discontinuation of zoledronic acid therapy [29]. A *post hoc* analysis was therefore performed to identify factors that predict fracture after 3 years of treatment and subgroups of patients who may

benefit from treatment continuation [41]. The analysis found that total hip or femoral neck BMD of  $\leq -2.5$ , and incident morphometric vertebral fracture during 3 years of zoledronic acid treatment were significantly associated with new morphometric vertebral fractures in the subsequent 3 years (p = 0.008, p = 0.0007 and p = 0.0156, respectively) [41].

#### Bone Mineral Density

BMD is the basis for osteoporosis diagnosis, according to the World Health Organization criteria, and has been shown to correlate with fracture risk [42]. It is commonly used as a surrogate endpoint for fracture risk.

**Alendronate.** In the FLEX study, 5 additional years of alendronate treatment maintained BMD at the total hip, femoral neck, trochanter, lumbar spine, total body and forearm compared with 5 years of alendronate followed by 5 years of placebo treatment (mean differences, 1.94–3.74%; p < 0.001 for all) [28]. Among patients who had received alendronate for 10 years, net gains in BMD relative to the FLEX baseline

285 were seen at the femoral neck, lumbar spine and total body  
286 (0.46–5.26%). Net loss of BMD at the total hip, trochanter and forearm  
287 during the FLEX study was reported in both groups, but the losses in  
288 the continuation group were significantly smaller than in the group  
289 that discontinued treatment for 5 years. For both groups, the BMD values  
290 at the femoral neck, lumbar spine, trochanter and total body at Year 10  
291 remained above the FIT baseline (Table 1). Similar results were seen in  
292 the 7-year extension study (10 years in total) of two phase III trials  
293 [35]; continued treatment with alendronate maintained BMD at all

294 sites measured; discontinuation of alendronate after Year 5 decreased  
295 BMD at the total hip, femoral neck and forearm, but BMD at the lumbar  
296 spine, trochanter, total hip and total body remained significantly above  
297 the original study baseline.

298 *Risedronate.* For risedronate, continuation of treatment for 2 additional  
299 years after 3 years of initial treatment continued to increase lumbar  
300 spine BMD, with BMD at all hip sites remaining stable (Table 1) [6].  
301 The second extension of VERT-MN also showed maintenance of

t1.1 **Table 1**

t1.2 Mean change in bone mineral density (BMD) in patients in long-term studies of bisphosphonate relative to pretreatment levels [6,29–31,33,35].

t1.3		BMD, %							
		Total hip		Femoral neck		Trochanter		Lumbar spine	
t1.4		Change from pretreatment	Mean difference (95% CI)	Change from pretreatment	Mean difference (95% CI)	Change from pretreatment	Mean difference (95% CI)	Change from pretreatment	Mean difference (95% CI)
t1.6	<i>Alendronate</i>								
t1.7	FLEX <sup>a</sup> [28]								
t1.8	ALN 10 years (n = 553) <sup>a</sup>	2.41	2.57 (1.78–3.36)***	4.75	NR	5.95	NR	14.80	3.81 (2.64–4.97)***
t1.9	ALN 5 years/PBO 5 years (n = 361) <sup>a</sup>	0.16		2.50		2.62		10.99	
t1.10	Extension study to two phase III studies (n = 44–80) <sup>b</sup> [35]								
t1.11	ALN 5 mg 10 years	2.6	NR	2.8	NR	4.8	NR	9.3	NR
t1.12	ALN 10 mg 10 years	6.7		5.4		10.3		13.7	
t1.13	ALN 5 years/PBO 5 years	3.4		1.5		5.3		9.3	
t1.14	<i>Risedronate</i>								
t1.15	VERT-MN first 2-year extension study <sup>c</sup> [6]								
t1.17	RIS 5 years (n = 130)	NR	NR	2.2	4.5	5.7	7.9	9.3	NR
t1.18	PBO 5 years (n = 135)	NR		NR		NR		NR	
t1.19	VERT-MN second 2-year extension study <sup>d</sup> [30]								
t1.20	RIS 7 years	3.9	NR	3.2	NR	6.1	NR	11.5	NR
t1.21	PBO 5 years/RIS 2 years	NR		NR		NR		6.1	
t1.22	<i>Ibandronate (oral)</i>								
t1.23	MOBILE extension <sup>e</sup> [33]								
t1.25	IBN 100 mg (n = 153)	3.0	NR	2.4	NR	5.6	NR	8.2	NR
t1.26	IBN 150 mg (n = 156)	3.5		3.2		6.0		8.4	
t1.27	<i>Ibandronate (intravenous)</i>								
t1.28	DIVA extension <sup>f</sup> [31]								
t1.29	IBN 2 mg q2 mo (n = 207)	3.0	NR	NR	NR	NR	NR	8.4	NR
t1.30	IBN 3 mg q3 mo (n = 228)	2.8		NR		NR		8.2	
t1.31									
t1.32	<i>Zoledronic acid</i>								
t1.33	HORIZON PFT extension study <sup>g</sup> [29]								
t1.34	ZOL 6 years (n = 450)	4.3	1.47 (0.80–2.14)***	4.5	1.36 (0.58–2.15)***	NR	NR	12.1	2.06 (–1.05–5.17) <sup>NS</sup>
t1.35	ZOL 3 years/PBO 3 years (n = 467)	2.8		3.1		NR		10.1	

t1.37 ALN, alendronate; BMD, bone mineral density; CI, confidence interval; DIVA, Dosing IntraVenous Administration; FIT, Fracture Intervention Trial; FLEX, Fracture intervention trial Long-term Extension; HORIZON PFT, Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly Pivotal Fracture Trial; IBN, ibandronate; LTE, long-term extension; MOBILE, Monthly Oral Ibandronate in LadiEs; NR, not reported; NS, not significant; PBO, placebo; RIS, risedronate; VERT-MN, Vertebral Efficacy with Risedronate Therapy Multinational; ZOL, zoledronic acid.

t1.38 <sup>a</sup> In FLEX, patients who received alendronate 5 or 10 mg for an average of 5 years in FIT received alendronate 5 or 10 mg (alendronate 10 years group) or placebo (alendronate/placebo group) for an additional 5 years. The numbers of patients shown are those with BMD measurements at Year 10. For lumbar spine BMD, ALN 5 years, n = 553; ALN 5 years/PBO 5 years, n = 365.

t1.39 <sup>b</sup> In this study, patients in the alendronate groups received alendronate 5 or 10 mg for 10 years. Patients in the alendronate/placebo group received alendronate 20 mg for the first 2 years, then alendronate 5 mg for 3 years followed by placebo for 4 years. The number of patients with BMD measurements from baseline to year 10 ranged from 44–49 for BMD at the total hip, 70–77 for BMD at the femoral neck, 69–76 for BMD at the trochanter and 70–80 for BMD at the lumbar spine.

t1.40 <sup>c</sup> In the first extension study of VERT-MN, patients continued their original regimen in VERT-MN for an additional 2 years. The numbers of patients shown are the total number included in this extension study. It was unclear if all patients have BMD measurements.

t1.41 <sup>d</sup> In the second extension study of VERT-MN, patients from the first extension study received risedronate for an additional 2 years. The numbers of patients with BMD measurements at the total hip were 54 for the RIS 7 years group, and 48 for the PBO 5 years/RIS 2 years group; at the lumbar spine the values of 'n' were 44 and 45, respectively. The numbers of patients with BMD measurements at the femoral neck and trochanter were not reported.

t1.42 <sup>e</sup> In this study, patients who had received monthly oral ibandronate 100 or 150 mg in the MOBILE study received the same regimen for an additional 3 years. For lumbar spine BMD: IBN 100 mg, n = 156; IBN 150 mg, n = 156.

t1.43 <sup>f</sup> In this study, patients who had received intravenous injections of ibandronate 2 mg bimonthly or 3 mg quarterly in the DIVA study received the same regimen for an additional 3 years. For lumbar spine BMD: IBN 2 mg, n = 208; IBN 3 mg, n = 230.

t1.44 <sup>g</sup> In the HORIZON PFT extension study, patients who received zoledronic acid for 3 years in the HORIZON PFT were randomized to receive zoledronic acid or placebo for an additional 3 years. The numbers of patients shown are those with BMD measurements at Year 6. For lumbar spine BMD: ZOL 6 years, n = 42; ZOL 3 years/PBO 3 years, n = 38.

t1.45 \*\*\* p < 0.001

302 lumbar spine BMD among those who had received risedronate for  
303 7 years [30].

304 *Ibandronate.* The MOBILE-LTE reported that 5 years of treatment with  
305 ibandronate 100 or 150 mg was associated with continued increases  
306 in BMD at the lumbar spine (2.2%–2.4% increase vs. extension study  
307 baseline) [33]. Mean total hip BMD decreased during the extension  
308 study for both doses (net loss of 0.3%–0.8%) but the magnitudes were  
309 small and not clinically relevant. Similar results were reported from  
310 the DIVA-LTE where continued treatment with ibandronate 2 mg  
311 bimonthly or 3 mg quarterly increased BMD lumbar spine relative to  
312 the extension study baseline (2.0% and 2.1%, respectively) [31]. For  
313 BMD at the total hip, femoral neck and trochanter, plateaus were  
314 reached after the third year of treatment (first year of the extension  
315 study) with the levels maintained out to 5 years. Small and clinically  
316 non-relevant decreases in mean total hip BMD relative to the DIVA-  
317 LTE baseline were seen at Year 5 for the 2 mg bimonthly group, and at  
318 Years 4 and 5 for the 3 mg quarterly group, but the mean total hip  
319 BMD levels remained above the DIVA core study baseline.

320 *Zoledronic acid.* The HORIZON PFT extension study of zoledronic acid  
321 showed that after 3 years of treatment, continuation for an additional  
322 3 years (6 years in total) maintained BMD at femoral neck, total hip  
323 and lumbar spine [29]. Relative to the HORIZON PFT extension baseline,  
324 continuation of zoledronic acid treatment for an additional 3 years was  
325 associated with a net 0.24% increase in femoral neck BMD, and 3.20%  
326 increase in lumbar spine BMD. This compared favorably with data from  
327 the discontinuation group in which a net loss of 0.80% and a net gain of  
328 1.18%, respectively, were observed ( $p \leq 0.002$  for both comparisons).  
329 As with alendronate, decreases in total hip BMD from the extension  
330 study baseline were seen in both groups with the continuation group  
331 showing significant benefits over the group that discontinued treatment  
332 ( $-0.36\%$  vs.  $-1.58\%$ ,  $p < 0.0001$ ). This maintenance of BMD was  
333 consistent with the open-label extension studies of zoledronic acid  
334 4 mg/year [43] in which the BMD levels at all sites were substantially  
335 above pretreatment levels, irrespective of whether patients continued  
336 or discontinued treatment after 3 years (Table 1). This provides  
337 confirmation of the residual benefits of zoledronic acid therapy, as  
338 observed in the fracture data.

### 339 Bone turnover markers

340 Bone turnover markers (BTMs) are commonly assessed as endpoints  
341 in trials of osteoporosis because elevated values have been associated  
342 with low BMD and increased risk of fractures in postmenopausal  
343 women [44]. Suppression of BTMs has been demonstrated in the pivotal  
344 studies of bisphosphonates [8,9,12,24–27], and the long-term effects of  
345 these agents on BTMs are investigated in the extension studies  
346 described below.

347 *Alendronate.* Women who continued alendronate treatment for 10 years  
348 in the FLEX study had stable levels of procollagen type I N-terminal  
349 propeptide (PINP),  $\beta$ -C-terminal telopeptide of type 1 collagen ( $\beta$ -CTX),  
350 and bone-specific alkaline phosphatase (BSAP) that were close to  
351 the FLEX baseline throughout the extension period [28]. There was a  
352 gradual increase in the levels of these markers over 5 years in women  
353 who discontinued alendronate but the levels remained below the  
354 pretreatment levels ( $-7\%$  for  $\beta$ -CTX and BSAP;  $-24\%$  for PINP). The  
355 7-year extension study (10 years in total) of the two identical phase III  
356 trials also found that continuation of alendronate treatment maintained  
357 the BTM reductions seen at the beginning of the treatment period, while  
358 treatment discontinuation led to small increases in BTM levels  
359 (including BSAP) that were still below the pretreatment values at the  
360 end of the extension period [35].

361 *Risedronate.* The VERT-MN extension studies also assessed BTM in  
362 patients receiving prolonged risedronate treatment [6,30]. In the first

2-year extension, patients who had received placebo for 5 years 363  
experienced a 5.9% median increase in BSAP from pretreatment baseline 364  
at Year 5, but subsequent treatment with risedronate for 2 years 365  
reduced BSAP to 23.0% below the pretreatment baseline. In contrast, 366  
patients who had received risedronate for 5 years experienced a 23.9% 367  
median BSAP reduction from pretreatment levels, and this reduction 368  
was maintained for 2 additional years of treatment during the extension 369  
study. Seven years of risedronate treatment also maintained a 54%–66% 370  
reduction in urinary N-terminal telopeptide (NTx) seen during the first 371  
3 months of VERT-MN core study. Modest urinary NTx suppression was 372  
also seen in the placebo group in VERT-MN but that could be due to the 373  
calcium and vitamin D supplementation that all patients received 374  
during the study [6]. 375

*Ibandronate.* A similar pattern was reported in the MOBILE extension 376  
study of oral ibandronate, in which rapid and pronounced decreases in 377  
 $\beta$ -CTX and PINP were seen at the initiation of treatment to Month 24 378  
and remained stable during the course of treatment for up to 5 years 379  
[33]. In the DIVA-LTE study, median  $\beta$ -CTX and PINP levels in patients 380  
who continued intravenous ibandronate treatment (2 mg bimonthly 381  
or 3 mg quarterly) increased during the 3-year extension study but 382  
the levels remained  $>30\%$  below the pretreatment values [31]. 383

*Zoledronic acid.* In the HORIZON PFT extension study, mean serum PINP 384  
rose slightly from the extension study baseline in both the treatment 385  
continuation (zoledronic acid treatment for 6 years,  $+19\%$ ) and 386  
discontinuation groups (zoledronic acid 3 years/placebo 3 years,  $+33\%$ ; 387  
difference,  $14\%$ ,  $p = 0.0001$ ), but the levels remained considerably 388  
below pretreatment values and within the postmenopausal reference 389  
range [29]. The mean levels of  $\beta$ -CTX and BSAP in both groups remained 390  
largely similar to those measured at the extension study baseline but 391  
sample sizes were too small to derive meaningful conclusions. 392

### 502 Long-term safety of bisphosphonate therapies 393

394 Safety analyses in long-term studies are of paramount importance 394  
because not all potential safety concerns can be identified during 3- 395  
year pivotal studies. Although postmarketing registry data may provide 396  
additional safety information about the use of a drug in clinical practice, 397  
results from these registries are often confounded by their retrospective 398  
and uncontrolled nature. Long-term safety data from randomized trials 399  
are, therefore, particularly important for therapies that may be used 400  
chronically. 401

### 402 Overall adverse event and serious adverse event reporting 402

403 *Alendronate.* In the two 10-year studies of alendronate, no significant 403  
differences in the incidence of adverse events (AEs), upper gastro- 404  
intestinal AEs, serious AEs (SAEs) or discontinuation due to AEs were 405  
reported between patients who continued treatment for 10 years versus 406  
those who discontinued treatment after 5 years [28,35,36]. For the 407  
extension study of two clinical trials, 4 deaths (details not provided) 408  
were reported among those who received alendronate 5 mg but none 409  
of these cases were considered to be associated with alendronate 410  
treatment [35]. 411

412 *Risedronate.* Five years of treatment with risedronate was associated 412  
with similar rates of AEs (including gastrointestinal AE), SAEs and 413  
withdrawal due to AEs, as placebo. The most common upper 414  
gastrointestinal AEs were dyspepsia and abdominal pain but the 415  
incidence of these AEs, and the incidence of moderate-to-severe cases, 416  
were similar between the treatment and placebo groups [6]. The second 417  
extension to the VERT-MN study also found no difference in the 418  
incidence of upper gastrointestinal AEs between those who had 419  
received risedronate for 7 years versus those who had received placebo 420  
for 5 years followed by risedronate for 2 years ( $9.6\%$  vs.  $8.6\%$ ) [30]. 421

*Ibandronate.* The MOBILE-LTE study reported hypertension, nasopharyngitis, back pain and arthralgia as the most commonly reported events in patients receiving oral ibandronate 100 or 150 mg for 5 years [33]. Gastrointestinal AEs were reported in 1.7% to 7.4% of patients and were the most common AEs considered to be related to ibandronate treatment. No clinically relevant changes in hematology or clinical chemistry were reported over the 5 years of treatment.

For intravenous ibandronate, the DIVA-LTE study showed a similar safety profile for the 2 mg bimonthly and 3 mg quarterly groups [31]. The most commonly reported AEs considered to be treatment-associated were gastrointestinal AEs (over 5 years: 2 mg bimonthly, 20%; 3 mg quarterly, 14%), including abdominal pain, dyspepsia, constipation and gastritis, and influenza-like symptoms (over 5 years: 2 mg bimonthly, 6.7%; 3 mg quarterly, 4.5%). Compared with the DIVA core study, no notable increase in the frequency of AEs was observed. The incidence of SAEs was also comparable between the two dosing groups (over 5 years: 2 mg bimonthly, 31%; 3 mg quarterly, 29%); the types of events reported included fractures, musculoskeletal and connective tissue disorders, myocardial infarctions and pneumonia.

*Zoledronic acid.* The HORIZON-PFT extension study of zoledronic acid also reported a comparable incidence of AEs (including post-dose symptoms), SAEs and deaths between patients who had received zoledronic acid treatment for 6 years and those who discontinued treatment after 3 years [29]. The incidence of post-dose symptoms, which were reported significantly more frequently in the zoledronic acid group than the placebo group in the core study [9], was similar in the continuation and discontinuation groups after each infusion during the extension study ( $p \geq 0.1$ ). This highlights the fact that post-dose symptoms are mainly a first-dose phenomenon.

#### 451 Target adverse event reporting

*Renal adverse effects.* As bisphosphonates are eliminated from the body through the kidneys, it is important to understand the effect of long-term use of bisphosphonates on renal function. All bisphosphonate therapies have warnings or contraindications for use in patients with severe renal impairment (creatinine clearance or estimated glomerular filtration rate [eGFR],  $<30$  or  $<35$  mL/min).

While renal safety data were not specifically described in the publication of the FLEX study of alendronate, a *post hoc* analysis of the FIT study showed that the incidence of renal AEs did not differ between patients with  $eGFR \geq 45$  mL/min versus those with  $eGFR < 45$  mL/min (2.3% vs. 2.1%,  $p = 0.68$ ). However, it was unclear how many patients reporting renal events received placebo or alendronate and, thus, few meaningful conclusions can be drawn from these results [45]. It should be noted, nevertheless, that the FIT (and therefore the FLEX) study excluded women with serum creatinine  $>1.27$  mg/dL.

Renal safety data were also not published for the extension studies of VERT-MN (risedronate). For ibandronate, eGFR showed no overall detrimental effect on renal function after 5 years of oral or intravenous ibandronate treatment [31,33]. However, a mean yearly decline in eGFR of 1.5 mL/min was observed over 5 years of intravenous ibandronate 2 mg bimonthly or 3 mg quarterly treatment.

Given that  $<1\%$  of bisphosphonate administered orally is absorbed, the maximal serum concentrations achieved after oral administration are much lower than those achieved after intravenous infusion. Consequently, the risk of tubular damage is higher with intravenous bisphosphonates, and cases of acute renal failure and renal injury requiring dialysis have been reported following zoledronic acid use, especially when the drug has been infused over a short period of time [46]. Hence, the recommended infusion time in the zoledronic acid label is no less than 15 min [19]. The label also includes a contraindication for patients with  $eGFR < 35$  mL/min. Use of this regimen in the core study was associated with no sign of long-term adverse effects on renal function after 3 yearly infusions [19,47]. In the

HORIZON PFT extension study, significantly more patients who continued zoledronic acid treatment for 6 years experienced transient increases in serum creatinine ( $>0.5$  mg/dL increase from baseline) compared with those who discontinued treatment after 3 years (2.94% vs. 0.65%,  $p = 0.002$ ) [29]. The majority of these increases occurred within 11 days after infusion and, in all subjects, this event resolved with no long-term impact on renal function. The mean change in serum creatinine from the extension baseline to the post-infusion follow-up visit was similar in both groups; there were also no between-group differences in mean change in eGFR

*Cardiovascular adverse events.* Cardiovascular AEs were not specifically communicated in the initial publications for the alendronate or risedronate extension studies [6,28,30,35,36] but, in a letter to the editors at the *New England Journal of Medicine*, Cummings et al. reported a numerical increase in atrial fibrillation SAEs in the alendronate arm ( $n = 47$ , 1.5%) compared with the placebo arm ( $n = 31$ , 1.0%) of the FIT study (relative hazard, 1.51;  $p = 0.07$ ) [48]. However, a later meta-analysis of 32 clinical trials of alendronate did not reveal any increased risk of atrial fibrillation [49]. For ibandronate, the MOBILE-LTE study reported cases of cardiovascular SAEs in patients who had received oral ibandronate 100 or 150 mg for 5 years [33]. These include angina pectoris (ibandronate 150 mg,  $n = 3$ ), myocardial ischemia (ibandronate 150 mg,  $n = 2$ ; 100 mg,  $n = 1$ ) and hypertension (ibandronate 150 mg,  $n = 2$ ; 100 mg,  $n = 1$ ). Myocardial infarction SAEs were also reported in the DIVA-LTE study of intravenous ibandronate but the cases were considered to be 'expected for an elderly population'.

In the HORIZON PFT core study, a significantly higher incidence of atrial fibrillation SAE was reported in the zoledronic acid group than in the placebo group (1.5% vs. 0.3%,  $p < 0.001$ ) [9]. This difference was, however, not replicated in subsequent studies. For example, the Recurrent Fracture Trial examined the effects of yearly zoledronic acid infusions on subsequent fractures after hip fracture. Although the cardiovascular risk profile of individuals enrolled in this study was worse than in the HORIZON PFT core study, the incidence of serious atrial fibrillation events was comparable between the two study arms (zoledronic acid, 1.1%; placebo, 1.3%;  $p = 0.84$ ) [50]. In the HORIZON PFT extension study, numerically more cases of atrial fibrillation AE (3.4% vs. 2.1%,  $p = 0.17$ ) and SAE (2.0% vs. 1.1%,  $p = 0.26$ ) were seen in those who received zoledronic acid for 6 years versus those who discontinued after 3 years but the differences did not reach statistical significance [29]. Stroke SAEs and deaths from stroke were also more common in the continuation group (0.7% and 3.1%) than the discontinuation group (0% and 1.5%) but the differences were not statistically significant ( $p = 0.06$  for both comparisons). This was seen in other HORIZON studies including the HORIZON PFT core study [9], in which stroke SAE and fatal stroke occurred at similar rates in the zoledronic acid and placebo groups (stroke SAE: zoledronic acid, 2.3%; placebo, 2.3%;  $p = 0.94$ ; fatal stroke: zoledronic acid, 0.5%; placebo, 0.3%;  $p = 0.15$ ). None of the stroke events in the HORIZON PFT extension study occurred within 30 days of infusion or were preceded by atrial fibrillation SAEs. Furthermore, significantly fewer patients in the continuation group reported hypertension compared with the discontinuation group (7.8% vs. 15.1%,  $p = 0.0001$ ). The investigators thus concluded that the data were uncertain and inconsistent, and that they do not support any general recommendations [29].

*Atypical fractures and osteonecrosis of the jaw.* Bisphosphonate use has been associated with an increased risk of atypical femur fractures [51–54]. However, these studies also pointed out that the absolute risk of atypical subtrochanteric fractures with bisphosphonate use is very low (approximately 1 in 1000 per year) [55], and treatment with bisphosphonates is not a prerequisite for the development of atypical fractures. The incidence of atypical fractures was not provided in the core publications of the long-term studies of alendronate, risedronate, or oral or intravenous ibandronate [6,28,30,31,33,35,36]. A *post hoc*

analysis of subtrochanteric or diaphyseal femur fractures was performed using data from 14,195 women in the FIT, FLEX and HORIZON PFT studies [56]. In the FLEX study, 4 fractures met the criteria for fracture of the subtrochanteric or diaphyseal femur. These fractures occurred in two women who had received alendronate for 10 years and one who had received alendronate for 5 years followed by placebo for 5 years. The relative hazard for fracture of the subtrochanteric or diaphyseal femur among subjects receiving alendronate, as compared with those receiving placebo, was 1.33 (95% CI, 0.12–14.67). In the HORIZON-PFT, 3 patients receiving zoledronic acid had fractures that met the location criteria, giving a relative hazard of 1.50 (95% CI, 0.25 to 9.00) for fracture of the subtrochanteric or diaphyseal femur in association with zoledronic acid use. No cases of atypical femur fracture, or hip or knee avascular necrosis were reported in the long-term study of zoledronic acid [29].

Osteonecrosis of the jaw (ONJ) is primarily associated with high-dose bisphosphonate treatment in patients with cancer [57,58], but a few reports have also documented the development of ONJ in osteoporosis patients treated with lower doses of bisphosphonate. For this reason, maxillofacial AEs were assessed objectively in the HORIZON-PFT extension study. There was one case of ONJ in a patient who had received zoledronic acid for 6 years in the HORIZON PFT extension trial, which resolved after appropriate treatment [29]. No cases of ONJ were reported for alendronate in the FLEX study, or for oral or intravenous ibandronate in the MOBILE- and DIVA-LTE studies [28,31,33].

It should be noted, however, that, owing to the rarity of these events, these long-term clinical trials were not powered to provide reliable incidence rates of atypical fractures or ONJ. Studies with longer observation periods may help to clarify the incidence of these conditions in patients receiving bisphosphonates for the treatment of osteoporosis.

### Clinical implications of the long-term data of bisphosphonates

Fracture prevention is the ultimate goal of long-term osteoporosis treatment, yet fracture risk assessments are difficult to perform in extension studies. Firstly, it may not be ethical to assign patients at risk of osteoporotic fractures to placebo arms and thus fracture risk reduction may not be assessed. Secondly, the natural attrition of the study population may substantially affect the power of fracture risk analyses. The majority of the long-term studies of bisphosphonates assessed fracture incidences as exploratory endpoints [6,28–30]. These are informative but the relevance of the results may be limited by the statistical power.

The FLEX and HORIZON PFT extension studies shared similar study designs that not only looked at the long-term antifracture effects of alendronate and zoledronic acid, but also the residual fracture protection after treatment discontinuation. Both studies showed that treatment continuation with alendronate or zoledronic acid beyond 5 or 3 years, respectively, was associated with continued significant vertebral fracture risk reduction, suggesting persistent antifracture effects beyond the 3-year pivotal trials. However, the types of fracture affected by treatment continuation were not consistent between the FLEX and HORIZON PFT extension studies. The former reported that treatment continuation significantly benefited clinical vertebral fractures, whereas the latter benefited morphometric vertebral fractures [15,28,29]. This difference is most probably explained by the small size of the study population and it is still unclear whether this suggests any differential efficacy between the two drugs.

As residual fracture benefits were observed in patients up to 5 years after discontinuation of alendronate therapy and up to 3 years after discontinuation of zoledronic acid therapy, the inevitable question is whether some patients may be able to discontinue treatment or go on a drug holiday after a few years of alendronate or zoledronic acid treatment without increasing their risk of fracture. *Post hoc* analyses from both the FLEX and the long-term study of zoledronic acid suggest that patients who still have low femoral neck BMD (T-score < -2.5)

after 3 to 5 years of treatment are at increased risk of vertebral fractures and may benefit most from continuation of bisphosphonate therapy [14]. Patients who develop new vertebral fractures during treatment also seem to benefit from continued therapy. However, it should be noted that this has been demonstrated in the zoledronic acid analysis but not in the alendronate analysis [14]. Therefore, patients with a BMD T-score > -2.5 after 3 to 5 years of treatment may potentially consider discontinuation of drug with continued appropriate monitoring. However, those with a BMD T-score < -2.5 or who have suffered a new fracture while on treatment should continue therapy. The duration of treatment and discontinuation of drug should be personalized for individual patients based on their response to treatment, fracture risk and comorbidities—no trial data provide guidance on this issue. Given that *post hoc* analyses of both zoledronic acid and alendronate suggest a correlation between low BMD and subsequent fracture risk, we suggest that BMD monitoring and fracture risk assessment should be carried out every year or every second year after discontinuation as criteria for potential treatment cessation in patients who are receiving bisphosphonates, and for reinitiation in those who have discontinued active treatment. Changes in BTM may also be useful in reflecting the residual effect of bisphosphonate in patients who have discontinued bisphosphonate treatment [59]. It should be noted, however, that the utility of basing treatment decisions on BMD and BTM levels has not been evaluated in prospective trials. However, based on the relationships between BMD or BTMs and fracture risk established in both the FIT and HORIZON studies, we suggest the following monitoring strategy: in patients who have discontinued osteoporosis treatment, a significant decrease in BMD (exceeding the least significant change, i.e. approximately 3–5%, depending on region of interest) or increase in BTMs (least significant change of approximately 25–30%) [60] suggests that the residual effect of the bisphosphonate therapy is diminishing and treatment reinitiation should be considered [59]. This strategy, however, will need to be validated in prospective studies. Furthermore, the statistical power of the *post hoc* analyses of long-term studies may be limited as they were based on subgroups of patients in studies of alendronate or zoledronic acid, and the results may or may not be extrapolated to other bisphosphonates. Long-term fracture data of other bisphosphonate therapies are limited: the size of the VERT-MN extension studies precludes meaningful conclusions about the long-term antifracture efficacy of risedronate and fracture results from oral and intravenous ibandronate treatment are lacking.

All long-term studies found that BMD at the hip increased during initial treatment and reached a plateau at around Year 3. Continued treatment maintained BMD at the hip while a gradual decline was observed among patients who discontinued treatment. Interestingly, all studies also found that long-term bisphosphonate treatment continued to increase BMD at the lumbar spine. This may be due to underlying spinal degenerative disease, which is common in postmenopausal women [61]. The implications of this observation remain unknown: a *post hoc* analysis of FLEX did not find any significant association between lumbar spine BMD and vertebral or nonvertebral fractures [40]; only a small subgroup of patients in the HORIZON PFT had BMD measurements at the lumbar spine and hence the subgroup analysis of the potential ability of lumbar spine BMD to predict vertebral fracture risk was not performed.

It is reassuring that discontinuation of alendronate and zoledronic acid treatment, according to the FLEX and the HORIZON PFT extension studies, respectively, was associated with only a small gradual increase of BTM within the postmenopausal range. This is important because a rebound of BTM to above pretreatment values has been reported in patients who had received non-bisphosphonate therapies for osteoporosis [62]. The BTM suppression with bisphosphonate treatment was most pronounced during the treatment initiation period, leveled off after approximately 3 years of treatment and remained relatively stable as treatment continued beyond 3 years. This shows that BTM

679 suppression is unlikely to increase over time if bisphosphonate use is  
680 continued beyond Year 3.

681 Long-term efficacy must be balanced with potential safety concerns.  
682 Safety data were, unfortunately, not reported comprehensively and  
683 consistently across extension studies of bisphosphonates. For instance,  
684 detailed safety results are not available for risedronate, and the data  
685 included in this paper are largely focused on those reported from the  
686 HORIZON PFT and *post hoc* analyses. Nonetheless, no unexpected AEs  
687 were identified in these studies and the long-term tolerability profiles  
688 of bisphosphonates remain favorable.

689 All bisphosphonate therapies carry warnings or contraindications  
690 relating to use in patients with reduced renal function (eGFR <30 or  
691 35 mL/min) and the renal safety of bisphosphonates has been reviewed  
692 recently [63]. An annual decline in eGFR was reported in association  
693 with intravenous ibandronate use but no long-term impact was noted  
694 [31]. Continued use of zoledronic acid for up to 6 years also showed no  
695 sustained impact on renal function but may be associated with transient  
696 increases in serum creatinine >0.5 mg/dL. It is, nevertheless, important  
697 to highlight that zoledronic acid is contraindicated in patients with  
698 eGFR < 35 mL/min and the medication should be infused over no less  
699 than 15 min, as per the product label [19].

700 Only one case of ONJ was reported in a long-term study of zoledronic  
701 acid, but clinicians should be aware that long-term bisphosphonate use  
702 may be associated with a low risk of ONJ, particularly in patients with  
703 cancer or those receiving glucocorticoid therapies [58]. As discussed in  
704 a recent report on subtrochanteric fractures (typical or atypical) after  
705 long-term bisphosphonate treatment [55], the incidence of these  
706 fractures following bisphosphonate treatment is low and no atypical  
707 femur fractures were identified in any of the long-term extension  
708 studies of bisphosphonates.

## 709 Conclusions

710 Clinical studies have shown that long-term use of bisphosphonates  
711 in postmenopausal women has persistent beneficial effects on fracture  
712 risk and BMD beyond 3 years of treatment. No unexpected AEs  
713 emerging from long-term treatment were identified in these studies  
714 and the long-term tolerability profiles of bisphosphonates remain  
715 favorable. Data from the two withdrawal extension studies of  
716 alendronate and zoledronic acid have also demonstrated residual  
717 fracture benefits in patients who discontinued treatment for 3 to  
718 5 years. It has been suggested that patients at high risk of fracture  
719 who have low BMD (T-score < -2.5) and/or an incident vertebral  
720 fractures after 3 to 5 years of treatment may benefit most from  
721 continuation of bisphosphonates. On the other hand, treatment  
722 discontinuation may be considered for patients at low risk for fracture  
723 who have achieved a BMD T-score > -2.5 after 3 to 5 years of treatment.  
724 Fracture risk assessments should be conducted regularly to determine  
725 whether treatment could be stopped or whether it should be  
726 reinitiated. The duration of treatment and possible discontinuation of  
727 treatment should be personalized for individual patients based on  
728 their response to treatment, fracture risk and comorbidities. Although  
729 comparable data in men are lacking, there are no reasons to suggest a  
730 different therapeutic strategy in male osteoporosis. However, firm  
731 recommendations regarding the criteria and timing of treatment  
732 reinitiation must await further research and investigations based on  
733 prospective randomized studies.

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