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Odanacatib: a review of its potential in the management of osteoporosis in postmenopausal women

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***Abstract*:** Odanacatib is a cathepsin K inhibitor developed for the treatment of postmenopausal osteoporosis. It is a bone resorption inhibitor, but which preserves bone formation to some extent. It can be administered once a week, in tablets also containing vitamin D. In a large clinical development program, it has been shown that odanacatib reduces bone resorption, with a reduction of about 60–70% in biochemical markers of resorption, while bone formation decreases to a lesser magnitude. Odanacatib continuously increases bone mineral density (BMD) at the hip and lumbar spine over 5 years. Once it is stopped, a complete resolution of effect is observed, with declining BMD and increased bone turnover. Bone microarchitecture and bone strength have also been improved in clinical trials using quantitative computed tomography (QCT) at the lumbar spine and hip, and high resolution peripheral QCT at the distal radius and tibia. In a phase III trial involving 16,713 postmenopausal women ⩾65 years of age with low BMD, the risk of fragility fracture was significantly reduced at the spine, hip and other nonvertebral sites compared with the placebo group. Odanacatib has been generally well tolerated, with no observation of osteonecrosis of the jaw so far, but with exceptional observations of subtrochanteric atypical fracture and morphea-like lesions. Odanacatib appears a useful new option in the treatment of postmenopausal osteoporosis.

Keywords: cathepsin K, fracture, odanacatib, osteoporosis

Introduction

Osteoporosis is a systemic disease of bone due to impaired bone strength, with an increased risk of low-energy fracture (i.e. the energy equivalent to a fall from standing height, or less) [NIH, 2001]. Roughly two-thirds of osteoporotic fractures are observed in postmenopausal women. Osteoporosis is a major health issue because the occurrence of certain types of fractures (hip, vertebra, upper humerus, pelvis, upper leg, several simultaneous ribs) increases mortality [Bliuc *et al.* 2009] and is responsible for substantial disability. Also, the incidence of fracture increases as the population ages, so that the absolute number of fractures is expected to rise significantly with aging of the population worldwide, even if the secular trend of age-adjusted incidence is currently slightly downward [Omsland and Magnus, 2014].

Several families of drugs have been made available to reduce the risk of osteoporotic fracture. Antiresorptive agents include bisphosphonates [Black *et al.* 1996, 2007; Cummings *et al.* 1998; Harris *et al.* 1999; McClung *et al.* 2001; Chestnut *et al.* 2004], denosumab [Cummings *et al.* 2009] and selective estrogen receptor modulators (SERMs) such as raloxifene and bazedoxifene [Delmas *et al.* 2002]. Two anabolic agents have been marketed so far, including teriparatide [Neer *et al.* 2001] and intact parathyroid hormone in a few countries [Greenspan *et al.* 2007]. Strontium ranelate is a compound improving bone strength by incorporating into the bone matrix [Meunier *et al.* 2004; Reginster *et al.* 2005]. All these drugs have shown relative risk reduction of vertebral fracture ranging from 40 to 65%, whereas the effect on nonvertebral fracture is lower, at around 20%, or even not apparent with SERMs. Relative risk reductions in hip fracture reached 40% with zoledronic acid and denosumab, but were lower or null with other agents.

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The use of anti-osteoporosis drugs has been associated with adverse events including thromboembolism with SERMs and strontium ranelate, rare atypical subtrochanteric fracture, and rare osteonecrosis of the jaw (ONJ) with bisphosphonates and denosumab. The widely publicized issue of ONJ has probably contributed to the decline in the prescription of anti-osteoporosis drugs that has been observed in recent years in various countries, even if their risk–benefit ratio remains favorable [Kanis *et al*. 2014; Solomon *et al*. 2014].

In this context, the development of a new class of anti-osteoporosis drug is welcome to improve fracture management. Here, we review the data regarding the treatment of postmenopausal osteoporosis using a cathepsin K inhibitor, odanacatib.

What is a cathepsin K inhibitor?

Osteoclasts express various enzymes for the degradation of bone matrix, including cathepsin K (CatK), a lysosomal cysteine proteinase. Cat K exhibits a high collagenase activity, especially at the acidic pH that is required to dissolve bone calcium hydroxyapatite. Pycnodysostosis, which is due to inactivating mutations of CatK in humans, leads to an increase in bone mass [Chavassieux *et al.* 2008], but is also associated with an increased risk of fragility fracture, in particular atypical subtrochanteric fracture of the femur, suggesting that the bone quality is impaired. Reductions in biochemical markers of bone resorption and increased bone mineral density (BMD) have been shown by pharmacological inhibition of CatK in rats and monkeys [Barrett *et al.* 2005; Kumar *et al.* 2007]. Non lysosomotropic inhibitors may be better than lysosomotropic inhibitors because they do not accumulate in the lysosomes of all cells. Lysosomal accumulation of drugs may be responsible for cross-inhibition of multiple cathepsins, in various tissues, leading to extraskeletal adverse events [Duong, 2012]. Basic compounds are more potent than nonbasic compounds in suppressing osteoclastic bone resorption [Fuller *et al.* 2010] for a longer duration, without effect on selectivity of the CatK inhibition.

A CatK inhibitor has to be selective over cathepsins B, L and S, which degrade collagen in other tissues such as the skin and the lung, to avoid side effects such as morphea-like skin reactions and respiratory abnormalities. In *in vitro* assays, odanacatib displayed greater potency to inhibit bone resorption and a greater selectivity towards other cathepsins than do other CatK inhibitors.

Pharmacokinetics of odanacatib

The plasma halflife of odanacatib is variable across species [Kassahun *et al.* 2011]. A longer plasma halflife has been observed in rhesus monkeys and dogs, as opposed to rats. The oral bioavailability depends on the vehicle and the species. In these preclinical species, biliary excretion is the most important mode of elimination. In rats and dogs, metabolism is a major way of elimination. In monkeys, odanacatib is almost completely eliminated by metabolism.

Two double-blind, randomized, placebo-controlled phase I studies have been conducted in postmenopausal women [Stoch *et al.* 2009]. They received odanacatib once weekly for 3 weeks (at doses of 5, 25, 50 or 100 mg) or once daily for 21 days (at doses of 0.5, 2.5 or 10 mg). In these studies, odanacatib was well tolerated. The long halflife ($t1_{/2}$ 66–93 hours) was found to be compatible with once-weekly dosing. Odanacatib exhibited sustained suppression of bone resorption biomarkers [C-terminal telopeptide (CTX) and N-terminal telopeptide (NTX)/creatinine (Cr)] at weekly doses $\geqslant$25 mg and daily doses $\geqslant$2.5 mg. But at low weekly doses (3 mg), the level of bone turnover and BMD loss is comparable with that observed in placebo-treated patients, suggesting that the inhibition may not be sustained over 1 week with a small dose [Eisman *et al.* 2011].

Effects of odanacatib in preclinical models

Osteoclastogenesis and survival of osteoclasts are not affected by CatK inhibition, as demonstrated from bone marrow of CatK−/− mice [Li *et al.* 2006; Pennypacker *et al*. 2009] or human osteoclast progenitors treated with odanacatib [Everts *et al.* 1985]. Odanacatib, however, decreases bone resorption activity as measured by CTX release or the resorption area. Osteoclasts treated with odanacatib form small shallow pits, in contrast with untreated cells which generate deep resorption lacunae. CatK and tartrate-resistant acid phosphatase (TRAP) positive intracellular vesicles accumulate toward the basolateral and functional secretory membranes of the polarized osteoclast, with TRAP(+) vesicles evenly distributed in the cytoplasm, suggesting that odanacatib disrupts multiple vesicular trafficking pathways [Leung *et al.* 2011]. The rapid kinetics

of inhibition and reversibility of the effects of odanacatib on bone resorption have been demonstrated in mature human osteoclasts on bone slices [Zhuo *et al.* 2014]. Odanacatib treatment in primates has been shown to increase osteoclast numbers [Masarachia *et al.* 2012], even if the exact cellular mechanism is not completely understood. This is consistent with the observation made in the odanacatib phase II clinical study showing that the osteoclast marker TRAP5b was increasing after 3 years of treatment.

When odanacatib has been administered in food to achieve steady-state exposures of 4 or 9 μM/day in ovariectomized rabbits for 27 weeks, which were compared with sham animals and alendronate treated rabbits [Pennypacker *et al.* 2011], odanacatib prevented lumbar vertebra BMD loss to levels comparable with the BMD observed in sham and alendronate-treated animals. BMD also increased dose-dependently at the femur. Mechanical properties were improved at the femur and spine. Of note, odanacatib did not reduce bone formation at any bone sites, which could have been anticipated because of the inhibition of bone resorption. It is likely that bone formation is preserved despite the bone resorption inhibition because signaling between osteoclasts and osteoblasts persists. Genetic studies have shown that bone formation is at least in part regulated by osteoclastic cells, providing evidence for a coupling mechanism *in vivo*. Also, *in vitro* studies have established S1P as a key osteoclast-derived coupling messenger, synthesized and secreted by osteoclasts, which promotes osteoblast differentiation and acts locally to stimulate the osteoblasts' bone anabolic activity. In addition, the presence and/or activity of CatK within osteoclasts represses the expression of Sphk1, and therefore the synthesis of S1P, thereby decreasing the ability of osteoclasts to stimulate bone formation [Lotinun *et al.* 2013].

In ovariectomized adult rhesus monkeys, odanacatib increased hip bone mass and cortical thickness by preserving endocortical bone formation and allowing for periosteal bone formation. Vertebral bone mass was also increased. The failure load was also improved at these two skeletal sites [Cusick *et al.* 2012; Masarachia *et al.* 2012]. In a head-to-head comparison with alendronate conducted in these monkeys, a greater improvement of hip bone mass, cortical thickness and finite element analysis (FEA) estimated bone strength at the distal radius was obtained with odanacatib [Williams *et al.* 2013; Cabal *et al.* 2013].

Effect of odanacatib in postmenopausal osteoporotic women

A 1-year dose-finding trial, followed by a 1-year extension on the same drug, assignment has been conducted in 399 postmenopausal women with low BMD to assess the effects of weekly doses of placebo or 3, 10, 25 or 50 mg of odanacatib on BMD and biochemical markers of bone remodeling [Bone *et al.* 2010]. The T-scores of these patients ranged between -2.0 and -3.5 at the spine or hip. All patients received calcium and vitamin D supplements. Over 24 months, odanacatib use was associated with dose-related increases in BMD. With the 50 mg dose of odanacatib, lumbar spine and total hip BMD increased by 5.5% and 3.2%, respectively, contrasting with stable BMD at these sites in patients on placebo. Biochemical markers of bone resorption decreased substantially, whereas markers of bone formation were more modestly decreased, suggesting a partial preservation of bone formation. Moreover, if the level of bone formation markers declined in the early phase of treatment, it tended to return to pretreatment values after 12 months of therapy with odanacatib. This trend parallels the evolution of TRAP5b, which reflects the number of osteoclasts that are accumulating. These osteoclastic cells may stimulate the osteoblasts *via* the clastokine S1P. The safety and tolerability of odanacatib were generally similar to those of placebo.

Among the 280 women who completed the second year extension, 189 were re-randomized to odanacatib 50 mg weekly or placebo for an additional year [Eisman *et al.* 2011]. BMD continued to increase during the third year of treatment with odanacatib 50 mg, both at the total hip (5.8% over 3 years) and spine (7.9% over 3 years). Urinary NTX remained reduced at year 3 (-50%), whereas bone-specific alkaline phosphatase (BSAP) was unchanged from baseline. Bone loss resumed at all sites after treatment was stopped. All bone turnover markers increased transiently above baseline after odanacatib was discontinued at the end of year 2, but this increase largely resolved by the end of year 3. The rates of adverse events were comparable in both treatment groups.

This preplanned extension was continued up to 5 years [Langdahl *et al.* 2013]. During years 4 and

5, women who had received placebo or odanacatib 3 mg in years 1–2 and placebo in year 3 received odanacatib 50 mg; others continued year 3 treatments. Spine and hip BMD increased continuously among the women who received odanacatib (10–50 mg) for 5 years. In the limited number of women (n = 13) who had been taking odanacatib continually for 5 years, mean lumbar spine BMD percentage change from baseline was 11.9%, compared with 0.4% among the women who were switched from odanacatib 50 mg to placebo after 2 years (n = 14). Women receiving dosage combinations of odanacatib (10–50 mg) for 5 years showed larger magnitude of reductions in bone resorption than that of bone formation markers. Resolution of effect was observed after discontinuation of odanacatib. Treatment with odanacatib for up to 5 years was generally well tolerated in this small group of patients.

The effect of odanacatib was compared with placebo in a small phase III trial dedicated to evaluating the effect of odanacatib with the latest bone imaging techniques including QCT at the hip and lumbar spine, and high resolution peripheral (HRp) QCT at the distal radius and tibia, along with the classical measures of areal BMD using dual energy X-ray absorptiometry (DXA) and of biochemical markers of bone turnover, among 214 postmenopausal with low areal BMD. As early as 6 months, odanacatib-treated women had greater increases in trabecular volumetric BMD and estimated compressive strength at the spine compared with placebo; integral and trabecular volumetric BMD and estimated strength at the hip also improved. At the femoral neck cortex, bone mineral content, thickness, volume and cross-sectional area also increased from baseline with odanacatib *versus* placebo over the entire course of the trial [Brixen *et al.* 2013]. At the distal radius and tibia, total volumetric BMD (vBMD), trabecular vBMD, cortical vBMD, cortical thickness and strength estimated using FEA showed significantly greater improvements with odanacatib compared with placebo [Cheung *et al.* 2014]. At the hip, the trabecular and cortical compartment were similarly affected by the gains in bone mineral content [Engelke *et al.* 2015]. The magnitude of these microarchitectural changes is of the same order of magnitude as with bisphosphonates when evaluated the same way, although no head-to-head comparison has been made.

In another trial, the effect of odanacatib taken after alendronate has been examined. In this randomized, double-blind, placebo-controlled, 24-month study, 243 postmenopausal women aged at least 60 years, with low BMD at the total hip, femoral neck or trochanter (T score $\leqslant -2.5$ but > -3.5 without prior fracture or $\leqslant -1.5$ but > -3.5 with prior fracture) who had taken alendronate for $\geqslant 3$ years were allocated to receive odanacatib or placebo [Bonnick *et al.* 2013]. In the odanacatib group, BMD changes from baseline at the femoral neck, trochanter, total hip and lumbar spine at 24 months (1.7%, 1.8%, 0.8% and 2.3%, respectively) were significantly different from the group switched to placebo, but the variation at the radius did not differ significantly between the two groups. As in prior reports of bisphosphonate-naïve patients, urinary NTX decreased with odanacatib. The level of beta CTX, however, increased unexpectedly. This might be explained by predominantly metalloproteinase-mediated bone resorption of older bone, which predominates in case of inhibition of CatK, while the inhibition of the resorption of younger bone seemed to continue, as shown by reduced levels of alpha CTX [Bonnick *et al.* 2013].

The main outcome for registration of anti-osteoporosis drugs is the reduction in fracture incidence. A phase III trial – still unpublished and only presented in a scientific meeting – involving 16,713 postmenopausal women $\geqslant 65$ years of age with low BMD has been conducted to prove the antifracture efficacy of odanacatib. Women were randomized to receive weekly odanacatib 50 mg or placebo for 3 years. The primary outcomes were time to first morphometric (radiographically assessed) vertebral fracture, time to first hip fracture and time to first clinical nonvertebral fracture. This trial was event-driven, so that it has been stopped after an interim analysis has shown robust reduction in vertebral and hip fracture incidence. The mean age at enrolment was 72 and 46% of these women had at least one prevalent vertebral fracture. There was a 54% relative risk reduction of new and worsening morphometric vertebral fractures, a 47% relative risk reduction of clinical hip fractures, a 23% relative risk reduction of clinical nonvertebral fractures and a 72% relative risk reduction of clinical vertebral fractures.

The adverse events were generally similar in the two groups, with the exception of diarrhea and pain in extremities, which were significantly more common in women on odanacatib. A few other adverse events that were not significantly

different between groups were also observed. The careful specific monitoring adjudicated 12 morphea-like lesions in the odanacatib group *versus* 3 in the placebo group, over 3 to 36 months, corresponding to an incidence of 5/10,000 patients-years. A quick resolution was obtained in 8 out of 12 cases. Atypical femoral shaft fractures were also reported for five patients in the odanacatib group with none in the placebo group. The extension of follow up is still ongoing. The US Food and Drug Administration (FDA) submission is expected to occur in 2015 after gathering more follow-up data.

Clinical perspective

The clinical development program of odanacatib has established its antifracture efficacy at the vertebra and the peripheral sites. It is generally well tolerated. New drugs against osteoporosis have to establish clear advantages over current therapies, which are effective and inexpensive because mostly generics. Because there is no head-to-head comparison, it is difficult to set the place of odanacatib in the context of other compounds. Odanacatib has been tested only *versus* placebo, because this is a new class. In some countries, this may be a significant obstacle to obtain reimbursement, because head-to-head comparisons may be required by the authorities to establish the advantages of a new drug.

The relative risk reduction of fracture obtained with odanacatib seems comparable with the existing most widely prescribed drugs. In contrast to bisphosphonates, its use does not seem to be associated with an increased risk of ONJ, but it is only after prescription to large numbers of patients that this assumption can be confirmed, given the extremely low incidence of this adverse event when it occurs in biphosphonate- or denosumab-treated patients. This could be an advantage if this better safety can be established. The risk of subtrochanteric atypical fracture looks similar to that observed with bisphosphonates. The magnitude and significance of the observation of morphea-like lesions remains to be further understood, in particular with the upcoming long-term extension study results. In this context odanacatib could appear as a second-line therapy, after 3–5 years of generic bisphosphonates, when a therapeutic window is often considered. The continued increase in bone mass over time obtained with odanacatib supports such a strategy. Odanacatib could also be an alternative to bisphosphonates in the few countries where cost is not the main driver of therapeutic guidelines, or when these drugs are contra-indicated or poorly tolerated.

Conclusion

Odanacatib is a CatK inhibitor that is a potent antiresorptive agent, but with relative preservation of bone formation. It increases BMD continuously over 5 years, improves bone strength as assessed by FEA at the central and peripheral skeleton, and reduces the incidence of fragility fracture at the spine and nonvertebral sites, including the hip. We need the complete long-term results of the phase III trial to better understand how to establish its place among all the treatments of postmenopausal osteoporosis.

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Conflict of interest statement

The author has been an investigator in several clinical trials of odanacatib.

References

Barrett, D., Boncek, V., Catalano, J., Deaton, D., Hassell, A., Jurgensen, C. *et al.* (2005) P2-P3 conformationally constrained ketoamide-based inhibitors of cathepsin K. Bioorg. *Med Chem Lett* 15: 3540–3546.

Black, D., Cummings, S., Karpf, D., Cauley, J., Thompson, D., Nevitt, M. *et al.* (1996) Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet* 348: 1535–1541.

Black, D., Delmas, P., Eastell, R., Reid, I., Boonen, S., Cauley, J. *et al.* (2007) Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 356: 1809–1822.

Bliuc, D., Nguyen, N., Milch, V., Nguyen, T. and Eisman, J. (2009) Mortality risk associated with low trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA* 301: 513–521.

Bone, H., McClung, M., Roux, C., Recker, R., Eisman, J., Verbruggen, N. *et al.* (2010) Odanacatib, a cathepsin-K inhibitor for osteoporosis: a two-year study in postmenopausal women with low bone density. *J Bone Miner Res* 25: 937–947.

Bonnick, S., De Villiers, T., Odio, A, Palacios, S., Chapurlat, R., DaSilva, C. *et al.* (2013) Effects of Odanacatib on BMD and safety in the treatment of osteoporosis in postmenopausal women previously treated with alendronate – a randomized placebo-controlled trial. *J Clin Endocrinol Metab* 98: 4727–4735.

Brixen, K., Chapurlat, R., Cheung, A., Keaveny, T., Fuerst, T., Engelke, K. *et al.* (2013) Bone Density, turnover, and estimated strength in postmenopausal women treated with odanacatib: a randomized trial. *J Clin Endocrinol Metab* 98: 571–580.

Cabal, A., Jayakar, R., Sardesai, S., Phillips, E., Szumiloski, J., Posavec, D. *et al.* (2013) High-resolution peripheral quantitative computed tomography and finite element analysis of bone strength at the distal radius in ovariectomized adult rhesus monkey demonstrate efficacy of odanacatib and differentiation from alendronate. *Bone* 56: 497–505.

Chapurlat, R. (2013) Contributions and limitations of the FRAX tool. *Joint Bone Spine* 80: 355–357.

Chavassieux, P., Asser Karsdal, M., Segovia-Silvestre, T., Neutzsky-Wulff, A., Chapurlat, R. *et al.* (2008) Mechanisms of the anabolic effects of teriparatide on bone: insight from the treatment of a patient with pycnodysostosis. *J Bone Miner Res* 23: 1076–1083.

Chesnut, C. III, Skag, A., Christiansen, C., Recker, R., Stakkestad, J., Hoiseth, A. *et al.* (2004) Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 19: 1241–1249.

Cheung, A., Majumdar, S., Brixen, K., Chapurlat, R., Fuerst, T., Engelke, K. *et al.* (2014) Effects of odanacatib on the radius and tibia of postmenopausal women: improvements in bone geometry and estimated bone strength. *J Bone Miner Res* 29: 1786–1794.

Cummings, S., Black, D., Thompson, D., Applegate, W., Barrett-Connor, E., Musliner, T. *et al.* (1998) Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 280: 2077–2082.

Cummings, S., San Martin, J., McClung, M., Siris, E., Eastell, R., Reid, I. *et al.* (2009) Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 361:756–765.

Cusick, T., Chen, C., Pennypacker, B., Pickarski, M., Kimmel, D., Scott, B. *et al.* (2012) Odanacatib treatment increases hip bone mass and cortical thickness by preserving endocortical bone formation and stimulating periosteal bone formation in the ovariectomized adult rhesus monkey. *J Bone Min Res* 27: 524–537.

Delmas, P., Ensrud, K., Adachi, J., Harper, K., Sarkar, S., Gennari, C. *et al.* (2002) Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. *J Clin Endocrinol Metab* 87: 3609–3617.

Duong, L. (2012) Therapeutic inhibition of cathepsin K – reducing bone resorption while maintaining bon formation. *BoneKEy Rep* 1: 67.

Eisman, J., Bone, H., Hosking, D., McClung, M., Reid, I., Rizzoli, R. *et al.* (2011) Odanacatib in the treatment of postmenopausal women with low bone mineral density: three-year continued therapy and resolution of effect. *J Bone Miner Res* 26: 242–251.

Engelke, K., Fuerst, T., Dardzinski, B., Kornak, J., Ather, S., Genant, H. and de Papp, A. (2015) Odanacatib treatment affects trabecular and cortical bone in the femur of postmenopausal women - results of a 2-year placebo-controlled trial. *J Bone Miner Res* 30: 30–38.

Everts, V., Aronson, D. and Beertsen, W. (1985) Phagocytosis of bone collagen by osteoclasts in two cases of pycnodysostosis. *Calcif Tissue Int* 37: 25–31.

Fuller, K., Lindstrom, E., Edlund, M., Henderson, I., Grabowska, U., Szewczyk, K. *et al.* (2010) The resorptive apparatus of osteoclasts supports lysosomotropism and increases potency of basic *versus* non-basic inhibitors of cathepsin K. *Bone* 46: 1400–1407.

Greenspan, S., Bone, H., Ettinger, M., Hanley, D., Lindsay, R., Zanchetta, J. *et al.* (2007) Effect of recombinant human parathyroid hormone (1–84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. *Ann Int Med* 146: 326–339.

Harris, S., Watts, N., Genant, H., McKeever, C., Hangartner, T., Keller, M. *et al.* (1999) Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA* 282: 1344–1352.

Kanis, J., Svedbom, A., Harvey, N. and McCloskey, E. (2014) The osteoporosis treatment gap. *J Bone Miner Res* 29: 1926–1928.

Kassahun, K., Black, W., Nicoll-Griffith, D., McIntosh, I., Chauret, N., Day, S. *et al.* (2011) Pharmacokinetics and metabolism in rats, dogs, and monkeys of the cathepsin k inhibitor odanacatib: demethylation of a methylsulfonyl moiety as a major metabolic pathway. *DMD* 39: 1079–1087.

Kumar, S., Dare, L., Vasko-Moser, J., James, I., Blake, S., Rickard, D. *et al.* (2007) A highly potent inhibitor of cathepsin K (relacatib) reduces

biomarkers of bone resorption both in vitro and in an acute model of elevated bone turnover in vivo in monkeys. *Bone* 40: 122–131.

Langdahl, B., Binkley, N., Bone, H., Gilchrist, N., Resch, H., Rodriguez Portales, J. *et al.* (2013) Odanacatib in the treatment of postmenopausal women with low bone mineral density: 5 years of continued therapy in a phase 2 study. *J Bone Miner Res* 27: 2251–2258.

Leung, P., Pickarski, M., Zhuo, Y., Masarachia, P. and Duong, L. (2011) The effects of the cathepsin K inhibitor odanacatib on osteoclastic bone resorption and vesicular trafficking *Bone* 49: 623–635.

Li, C., Jepsen, K., Majeska, R., Zhang, J., Ni, R., Gelb, B. *et al.* (2006) Mice lacking cathepsin K maintain bone remodeling but develop bone fragility despite high bone mass. *J Bone Miner Res* 21: 865–875.

Lotinun, S., Kiviranta, R., Matsubara, T., Alzate, J., Neff, L., Luth, A. *et al.* (2013) Osteoclast-specific cathepsin K deletion stimulates S1P-dependent bone formation *J Clin Invest* 123: 666–681.

Masarachia, P., Pennypacker, B., Pickarski, M., Scott, K., Wesolowski, G., Smith, S. *et al.* (2012) Odanacatib reduces bone turnover and increases bone mass in the lumbar spine of skeletally mature ovariectomized rhesus monkeys. *J Bone Miner Res* 27: 509–523.

McClung, M., Geusens, P., Miller, P., Zippel, H., Bensen, W., Roux, C. *et al.* (2001) Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med* 344: 333–340.

Meunier, P., Roux, C., Seeman, E., Ortolani, S., Badurski, J., Spector, T. *et al.* (2004) The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 350: 459–468.

Neer, R., Arnaud, C., Zanchetta, J., Prince, R., Gaich, G., Reginster, J. *et al.* (2001) Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 344: 1434–1441.

NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis and Therapy (2001) Osteoporosis prevention, diagnosis, and therapy. *JAMA* 285: 785–795.

Omsland, T. and Magnus, J. (2014) Forecasting the burden of future postmenopausal hip fractures. *Osteoporos Int* 25: 2493–2496.

Pennypacker, B., Shea, M., Liu, Q., Masarachia, P., Saftig, P., Rodan, S. *et al.* (2009) Bone density, strength, and formation in adult cathepsin K (−/−) mice. *Bone* 44: 199–207.

Pennypacker, B., Le Duong, T., Cusick, T., Masarachia, P., Gentile, M., Gauthier, J. *et al.* (2011) Cathepsin K inhibitors prevent bone loss in estrogen-deficient rabbits. *J Bone Miner Res* 26: 252–262.

Reginster, J., Seeman, E., De Vernejoul, M., Adami, S., Compston, J., Phenekos, C. *et al.* (2005) Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. *J Clin Endocrinol Metab* 90: 2816–2822.

Solomon, D., Johnston, S., Boytsov, N., McMorrow, D., Lane, J. and Krohn, K. (2014) Osteoporosis medication use after hip fracture in U.S. patients between 2002 and 2011 *J Bone Miner Res* 29: 1929–1937.

Stoch, S., Zajic, S., Stone, J., Miller, F., van Dick, K., Guttierez, M. *et al.* (2009) Effect of the cathepsin k inhibitor odanacatib on bone resorption biomarkers in healthy postmenopausal women: two double-blind, randomized, placebo-controlled phase I studies. *Clin Pharmacol Ther* 86: 175–182.

Williams, D., McCracken, P, Purcell, M., Pickarski, M., Mathers, P., Savitz, A. *et al.* (2013) Effect of odanacatib on bone turnover markers, bone density and geometry of the spine and hip of ovariectomized monkeys: a head-to-head comparison with alendronate. *Bone* 56: 489–496.

Zhuo, Y., Gauthier, J, Black, W., Percival, M. and Duong, L. (2014) Inhibition of bone resorption by the cathepsin K inhibitor odanacatib is fully reversible. *Bone* 67: 269–280.