

TARGETING CATHEPSIN K FOR THE TREATMENT OF OSTEOPOROSIS: FOCUS ON ODANACATIB

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SUMMARY

Cathepsin K is a lysosomal cysteine protease expressed by osteoclasts that degrades type I collagen during the process of bone remodeling. Postmenopausal osteoporosis (PMO) is a disease of excessive bone turnover, with an imbalance between bone resorption and bone formation that causes loss of bone strength and increased risk of fractures. Medications that reduce bone turnover have been proven to reduce fracture risk in women with PMO. Inhibition of cathepsin K reduces bone resorption, with the potential of decreasing fracture risk in women with PMO. Odanacatib (MK-0822, MK-822) is an orally administered cathepsin K inhibitor that is currently in development for the treatment of osteoporosis. In a phase II clinical trial oral odanacatib increased bone mineral density (BMD) and reduced bone turnover markers more than placebo in postmenopausal women with low BMD, with no reports of intolerance or skeletal toxicity. A phase III clinical trial to evaluate the effects of odanacatib on fracture risk in women with PMO is currently under way and fully enrolled. Odanacatib is a promising emerging agent for the management of PMO and other skeletal disorders associated with excessive bone turnover.

INTRODUCTION

Bone remodeling is a physiological process by which the adult skeleton continually renews itself. Removal of small discrete packets of bone collagen and mineral occurs through the action of osteoclasts (bone-resorbing cells), followed by deposition of new collagen by osteoblasts (bone-forming cells) and subsequent mineralization of the collagen. When bone resorption and formation are well balanced, as typically occurs in healthy young adults, bone mineral

density (BMD) and bone strength are stable. If bone resorption exceeds bone formation, as occurs in postmenopausal estrogen-deficient women, there is a net loss of bone over time that may ultimately result in osteoporosis and increased risk of fractures (1). Osteoporosis is a common disease associated with increased morbidity, increased mortality and high healthcare costs due to fractures (2).

Bone resorption requires the attachment of an osteoclast to the bone surface by means of a "sealing zone" in order to create a self-contained compartment between the bone surface and the adjacent ruffled border of the osteoclast (3). The acidic microenvironment beneath the osteoclast demineralizes the bone and exposes the underlying matrix, which is then degraded through the action of cysteine proteases (4). Since cathepsin K is the most abundant cysteine protease expressed in osteoclasts and a rate-limiting factor for osteoclastic bone resorption (5), it has been identified as a potential target for the treatment of diseases associated with high bone resorption (6-8), such as postmenopausal osteoporosis (PMO). Cathepsin K and other cysteine proteases are secreted as inactive enzymes that require acidic conditions, as exist beneath osteoclasts attached to the bone surface (Fig. 1), for cleavage of the propeptide to form the active enzyme. Cathepsin K degrades type I collagen in the telopeptide regions, as well as at multiple locations on the triple helix.

The rationale for the clinical development of inhibitors of cathepsin K to treat osteoporosis is supported by animal studies. For example, there is evidence that cathepsin K knockout mice have increased BMD, thickened bone trabeculae and increased bone strength (9); transgenic mice with overexpression of cathepsin K have reduced trabecular bone volume due to accelerated bone turnover (10); compounds that inhibit cathepsin K reduce markers of bone resorption in ovariectomized (OVX) nonhuman primates (11) and increase BMD in OVX rabbits (12).

Cathepsin K deficiency in humans occurs in a rare autosomal recessive disorder called pycnodysostosis (13), thought to be present in the well-known 19th century French artist Henri Toulouse-Lautrec (14). Individuals with pycnodysostosis have short stature and dense bones (pycnos = dense), but typically suffer from low trauma fractures, while those who are heterozygous for this mutation are clinically normal (15). It has been suggested that skeletal fragility associated with pycnodysostosis may be the result of a profound

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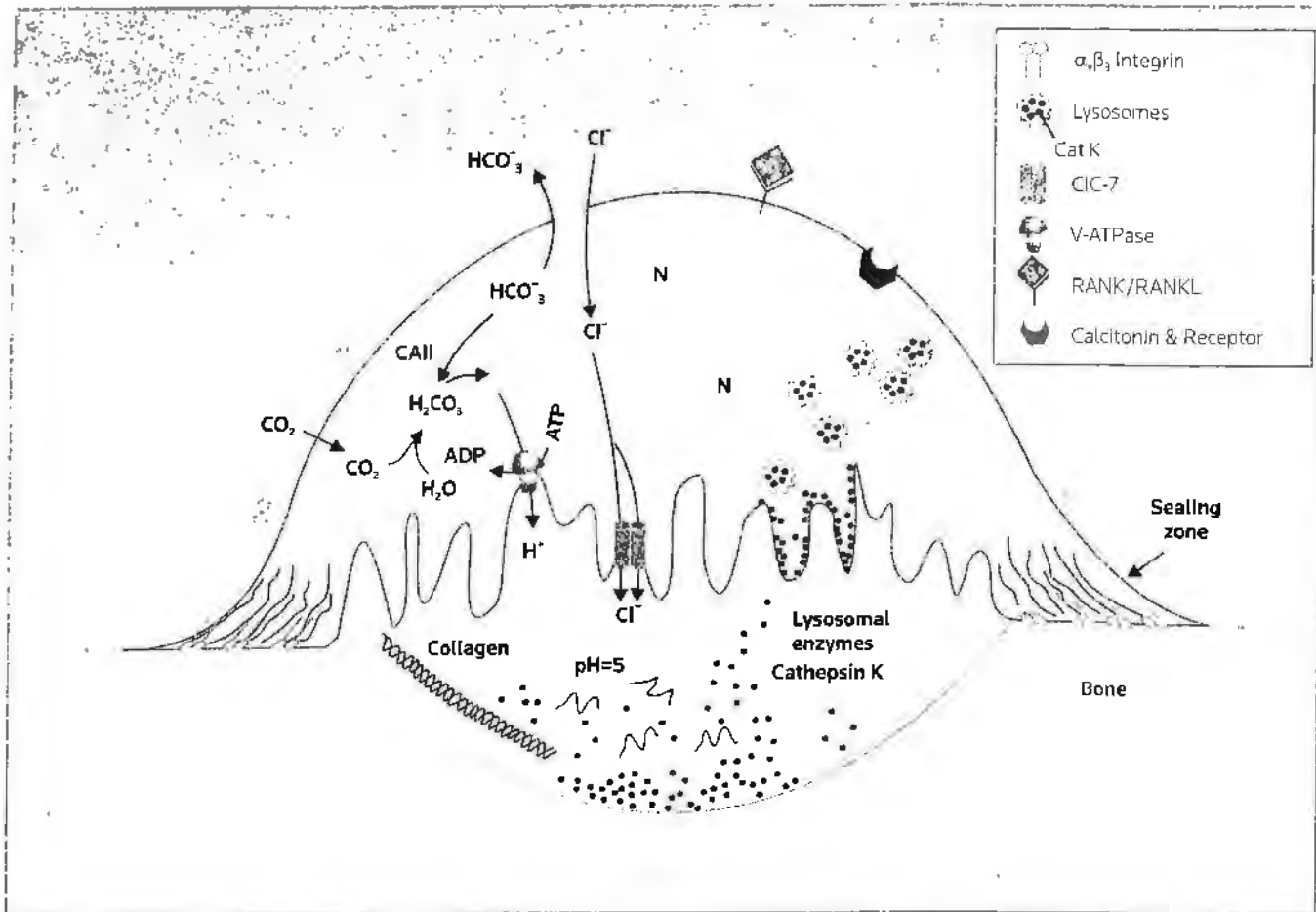


Figure 1. Schematic representation of a resorbing osteoclast. Demineralization is the result of acidification of the resorption lacuna due to secretion of H⁺ and Cl⁻ ions. Secreted lysosomal cathepsin K degrades type I collagen through cleavage of the N-terminal region and the triple helical structure of collagen molecules at multiple sites. From Rodan, S.B., Duong, L.T. *Cathepsin K - a new molecular target for osteoporosis*. *JBMS BoneKey*. 2008 January;5(1):16-24, with permission from the International Bone & Mineral Society.

decrease in bone remodeling, leading to a lack of microdamage removal, although there is no direct evidence for microdamage accumulation (16). Others have suggested that the increased susceptibility to fractures in these patients is due to osteomalacia that occurs concomitantly with increased BMD (17), similar to rickets, which has been paradoxically reported in patients with infantile malignant osteopetrosis (18).

A compound that reduces but does not eliminate cathepsin K might be expected to act as an antiresorptive agent with potentially beneficial skeletal effects. Antiresorptive agents that are currently approved for the management of PMO include four bisphosphonates (alendronate, risedronate, ibandronate, zoledronate), denosumab, raloxifene and nasal calcitonin. These agents have been shown to reduce bone resorption marker levels, stabilize or increase BMD, and reduce fracture risk. Despite proven efficacy and generally favorable safety profiles, their impact in reducing the burden of osteoporotic fractures has been disappointing (19) due to suboptimal compliance and persistence (20). Patients with poor compliance and persistence have a reduced BMD response (21), higher fracture

risk (22) and greater healthcare costs (23) than those with good compliance and persistence. There are many factors contributing to patients not taking medication correctly or sufficiently long to benefit (24). Among these are side effects of treatment or the fear of side effects that have not actually occurred. Oral bisphosphonates may cause upper gastrointestinal upset and intravenous bisphosphonates sometimes cause transient flu-like symptoms. Other events reported with bisphosphonate use, without clear evidence of a causal relationship or well-defined pathogenesis, include osteonecrosis of the jaw, atypical femur fractures, chronic musculoskeletal pain and atrial fibrillation (25). There have been theoretical concerns, without clear evidence of increased risk, over possible adverse immune effects with denosumab (26), a fully human monoclonal antibody to receptor activator of nuclear factor kappa-B ligand (RANKL), a cytokine member of the tumor necrosis factor (TNF) family that is the principal mediator of osteoclastic bone resorption. Raloxifene, a selective estrogen receptor modulator, may cause leg cramps, vasomotor symptoms and thromboembolic events, and increase the risk of fatal stroke in women at high risk for cardiovas-

cular disease (27). Nasal calcitonin is generally well tolerated except for nasal irritation and epistaxis in some patients (28), but appears to have the weakest antiresorptive effect of all approved agents. For all these reasons, there may be clinical utility in developing new therapeutic agents that expand the options for managing osteoporosis, with the hope of providing more choices for matching the risk/benefit profile of the drug with the circumstances of each individual patient.

There are currently no cathepsin K inhibitors approved for the treatment of osteoporosis. This is a review of cathepsin K inhibitors that have advanced to clinical testing, with a focus on odanacatib (MK-0822, MK-822; Merck & Co./Celera), the only cathepsin K inhibitor in phase III clinical trials for the treatment of PMO.

CATHEPSIN K INHIBITORS

As early as 1968, the idea was proposed that lysosomal acid hydrolases were responsible for the degradation of bone matrix (29). In 1984, *in vitro* and *in vivo* experiments showed that two inhibitors of lysosomal cysteine proteases, E-64 and leupeptin, reduced bone resorption (30). At that time, the identity of the enzyme or enzymes responsible for degradation of the bone matrix was not known. Cathepsins B and L were thought to be involved in the bone resorption process, but were not attractive targets for therapeutic intervention due to their expression in many cell types in addition to osteoclasts. It was not until 10 years later, in 1994, that cathepsin K was discovered and found to be predominantly expressed by osteoclasts (31), with lower expression in other cells, including macrophages, synovial fibroblasts, fibroblasts in areas of inflammation, chondrocytes, breast and prostate tumor cells (8). Cathepsin K is downregulated by estrogen (32) and upregulated by RANKL (33). Human cathepsin K is a protein consisting of 329 amino acids with an *N*-terminal sequence of 15 amino acids, a propeptide of 99 amino acids and a catalytic unit of 215 amino acids (34). The enzyme is sequestered in lysosomes and is secreted into the extracellular microenvironment beneath activated osteoclasts attached to the bone surface.

Potential adverse effects of cathepsin K inhibition may be caused by "off-target" inhibition of other cathepsins or by inhibition of cathepsin K in cells other than osteoclasts. Human cathepsin K deficiency (pseudohypoparathyroidism) is associated with accumulation of collagen fibrils in fibroblasts, as well as an abnormal phenotype, and rodent cathepsin K deficiency is associated with pulmonary fibrosis (35). In addition to potential effects of cathepsin K inhibition on the skin and lung, noncollagenous substrates may be affected. Cathepsin K-deficient mice have been observed to have learning disorders and cathepsin K deficiency in humans has been implicated in the pathogenesis of schizophrenia (36). These potential undesirable effects of cathepsin K inhibition remain poorly characterized, but must be considered in the development of drugs in this class for the treatment of osteoporosis.

There is potential benefit from inhibition of cathepsin K in the treatment of diseases other than osteoporosis. In animal models of rheumatoid arthritis, overexpression of cathepsin K is associated with spontaneous synovitis and cartilage erosion (37), raising the possibility that inhibition of cathepsin K might be useful in the treatment of rheumatoid arthritis in humans. Cathepsin K has also been

implicated in the pathogenesis of osteoarthritis, with the finding of accumulation of this enzyme in articular chondrocytes in a transgenic mouse model (38). Cathepsin K may play a role in the progression of atherosclerosis, suggesting that inhibition of cathepsin K might be beneficial for its treatment (39). Cathepsin K is upregulated in human tumor cells, including breast, lung, brain, bone, prostate and melanoma cells, and has been proposed as a potential therapeutic target for the treatment of cancer (40).

The ideal cathepsin K inhibitor should be a low-molecular-weight compound that binds reversibly and highly selectively without affecting other major cysteine proteases, particularly the closely related cathepsins L, S and V (36). Other desirable properties include oral bioavailability, long serum half-life, slow elimination rate and low toxicity. The drug must be delivered to lysosomes and/or resorption lacunae of osteoclasts, and/or to synovial fibroblasts as potential therapy for rheumatoid arthritis. Potential cathepsin K inhibitors can be screened for potency and selectivity using enzyme assays with purified recombinant human cathepsin K and other related cathepsins, such as L, B and S (8). Recent study of cathepsin K inhibitors has been directed to compounds that include peptidyl aldehydes, amides, α -keto heterocycles, aliphatic ketones and nitriles (41). The compounds that have advanced the furthest are balicatib (AAE-581; Novartis), relacatib (SB-462795; GlaxoSmithKline) and odanacatib. Of these, only odanacatib remains in development for the treatment of osteoporosis, with a large phase III clinical trial to evaluate its efficacy in reducing fracture risk currently ongoing. Other cathepsin K inhibitors of potential clinical interest include ONO-5334 (Ono Pharmaceutical), currently in a phase II trial in postmenopausal women with osteopenia or osteoporosis, VEL-0230 (Velcura Therapeutics), which has completed a phase I trial, and the candidate drugs MIV-710 and MIV-711 (Medivir Pharma).

Balicatib

Balicatib is a basic peptidic nitrile compound that is a potent inhibitor of human cathepsin K ($IC_{50} = 1.4$ nM) (42). In a 1-year, randomized, placebo-controlled trial in 675 postmenopausal women with low BMD (osteopenia/osteoporosis), daily oral balicatib (5, 10, 25 and 50 mg) was compared with placebo, with outcome measures that included BMD and bone turnover markers (43). At 12 months, there was a dose-related increase in BMD at the lumbar spine and total hip with balicatib compared with placebo that was statistically significant ($P < 0.0005$) with all doses except 5 mg/day. There was a dose-dependent and statistically significant decrease in markers of bone resorption (serum C-telopeptide cross-linked collagen type I [CTX], urine N-telopeptide cross-linked collagen type I [NTX]) with balicatib 25 and 50 mg/day compared with placebo; there was no significant change in markers of bone formation (serum bone-specific alkaline phosphatase [BSAP], osteocalcin, PINP) with balicatib 10, 25 and 50 mg/day compared with placebo, while there was a significant increase in bone formation marker levels with balicatib 5 mg/day. Balicatib was generally well tolerated at doses up to 25 mg/day. There was a higher incidence of dermatological adverse events (mainly pruritus) with the dose of 50 mg/day and a small number of patients reported to have scleroderma and morphea-like skin changes that resolved after stopping treatment. Clinical trials with balicatib were subsequently discontinued due to these types of adverse dermatological effects (36, 44). The skin disorders associat-

ed with balicatib may be a consequence of its lysosomotropic character, resulting in accumulation in lysosomes and nonselective off-target inhibition of other cathepsins, such as B and L, that are highly expressed in lysosomes of skin fibroblasts (36).

Relacatib

Relacatib is an orally bioavailable nonbasic 7-methyl-substituted azepanone analogue with high cathepsin K-inhibitory potency ($K_{i,app} = 41$ pM); however, its clinical application is limited due to its low selectivity, with evidence of inhibition of other cathepsins, including L, V, S and B (36). Clinical development of relacatib was reportedly halted after phase I studies (8).

Odanacatib

Preclinical development

In vitro studies have shown that odanacatib inhibited human cathepsin K with an IC_{50} of 0.20 nmol/L (3- to 4-fold more potent than balicatib and relacatib) and at least 300-fold greater selectivity over other known human cathepsins (45). Odanacatib was evaluated in a 21-month study in OVX adult rhesus monkeys aged 13-19 years who were dosed orally daily with either vehicle alone or odanacatib 6 or 30 mg/kg in 0.5% methocel (11, 46). BMD was measured quarterly, with biomechanical bone strength testing (3-point bending of the mid-femur, femoral neck shearing and vertebral body compression) and double tetracycline bone histomorphometry assessed after necropsy at the end of the study. A dose-dependent increase in BMD was observed in the odanacatib-treated animals, with improvement in parameters of bone strength and maintenance of normal bone quality. In a 28-week study in adult New Zealand white rabbits (aged 7 months), the animals were randomized to one of five groups: sham OVX + control diet, OVX + control diet, OVX + 0.0016% odanacatib diet, OVX + 0.004% odanacatib diet or OVX + control diet with alendronate 0.3 mg/kg s.c. twice a week (12). Assessments included BMD and dual calcein labeling done 10 and 3 days prior to necropsy. It was reported that odanacatib prevented estrogen deficiency bone loss in rabbits, with no suppression of bone formation parameters, whereas alendronate was associated with inhibition of bone formation.

Metabolism and pharmacokinetics

Odanacatib has demonstrated excellent metabolic stability in hepatocyte incubations in several animal species (45). In standard incubations, there was 96% recovery of parent compound in rat hepatocytes and 98% recovery in rhesus monkey hepatocytes. In both dog and human hepatocyte incubations recovery was > 99%.

The pharmacokinetics (PK) of odanacatib have been evaluated in preclinical studies in rats, dogs and rhesus monkeys (45). Oral bioavailability was found to be highly dependent on vehicle, dose and sample preparation. In dogs, for example, oral bioavailability was only 6% when dosed as a suspension in 0.5% methocel at 5 mg/kg, but it was 100% when dosed as an amorphous dispersion prepared by adding a PEG-200 solution of the compound to methocel with sonication. In rats, oral bioavailability was 38% with a dose of 5 mg/kg as a solution in PEG-400. The half-lives were reported to

be long in all species (6 h in rats, 57 h in monkeys and 18 h in rhesus monkeys), consistent with the observation of metabolic stability.

Two phase I studies in healthy postmenopausal women reported a serum half-life for odanacatib ranging from approximately 66 to 93 h with weekly or daily oral dosing (5). Weekly dosing was associated with moderate accumulation of 1.2- to 1.6-fold and a modest peak-to-trough concentration ratio of 3- to 5-fold. With daily dosing, greater accumulation (4- to 5-fold) was reported, with a flat concentration-time profile during the dosing interval. Trough concentration data suggested that steady-state conditions were achieved in the third week of dosing with both regimens. The PK profiles typically showed a primary peak with a time to maximal concentration of about 4-6 h, with a secondary peak often seen at about 24 h. On both the first and last days of dosing, the values for the area under the curve (AUC), peak plasma concentration (C_{max}) and $C_{168 h}$ increased approximately dose-proportionally from 0.5 to 10 mg, with PK being less than dose-proportional at doses of 25 mg and greater.

Phase I clinical trials

Two randomized, double-blind, placebo-controlled phase I studies of odanacatib have been reported (5) (Table I). In the daily dosing study (NCT00769418), 30 healthy postmenopausal women aged 70 or younger were randomized, with 24 assigned to receive oral odanacatib once daily for 21 days (0.5, 2.5 or 10 mg/dose) and 6 assigned to receive placebo once daily for 21 days. In the weekly dosing study (NCT00770159), 49 healthy postmenopausal women aged 75 or younger were randomized, with 37 assigned to receive oral odanacatib once weekly for 3 weeks (5, 25, 50 or 100 mg/dose) and 12 assigned to receive placebo once weekly for 3 weeks. Bone turnover markers, safety monitoring and plasma concentrations were assessed. Weekly dosing of odanacatib at the three highest doses (25, 50 and 100 mg) resulted in substantial reductions in the levels of serum CTX and urine NTX normalized to creatinine (NTX/Cr) (about 62% for each) that were sustained over the dosing interval. Daily dosing of odanacatib at the two highest doses (2.5 and 10 mg) resulted in significant reductions in CTX and NTX/Cr (up to 81% for each) beginning 3-5 days after starting treatment and continuing through day 24. The doses of 5 mg weekly and 0.5 mg daily resulted in only a slight reduction in bone resorption markers. No significant changes were observed in the two bone formation markers measured – serum BSAP and serum osteocalcin.

Phase II clinical trials

A randomized, double-blind, placebo-controlled, dose-ranging phase II study (NCT00112437) evaluated the effects of odanacatib in postmenopausal women with low BMD (47, 48). The subjects (N = 399; mean age: 64.2 ± 7.8 years) had a baseline BMD T-score of -2.0 or less at the lumbar spine, femoral neck, trochanter or total hip, and of -3.5 or greater at all skeletal sites measured. They were randomized to receive weekly oral odanacatib (3, 10, 25 or 50 mg) or placebo. All participants received daily supplemental calcium 500 mg if daily intake was < 1000 mg and weekly vitamin D₃ 5600 IU. The primary endpoint was the percent change in lumbar spine BMD compared to baseline, with other endpoints including percent change in BMD at the proximal femur, total body and distal forearm

Table 1. Summary of key randomized, double-blind, placebo-controlled clinical trials of odanacatib in postmenopausal women.

Phase	Ref.	NCT ID	Odanacatib dose (oral)	N	Subjects	Primary endpoint	Results/comments
I	5	NCT00769418	0.5, 2.5, 10 mg daily	30	Healthy postmenopausal women aged ≤ 70 years	Safety and tolerability of multiple daily oral doses for 21 days	Dose-dependent suppression of markers of bone resorption; well tolerated; favorable safety profile
I	5	NCT00770159	5, 25, 50, 100 mg weekly	49	Healthy postmenopausal women aged ≤ 75 years	Safety and tolerability of multiple weekly oral doses for 21 days	Dose-dependent suppression of markers of bone resorption; well tolerated; favorable safety profile
II	37, 38	NCT00112437	3, 10, 25, 50 mg weekly	399	Postmenopausal women between 45 and 85 years with low BMD (T-score ≤ -2.0)	Percent change from baseline in lumbar spine BMD. Twelve-month study with planned extension of 24 months	Dose-dependent increase in lumbar spine and hip BMD; suppression of bone turnover markers; safety and tolerability similar to placebo
III	39	NCT00729183	50 mg weekly	180	Postmenopausal women aged 45-85 years with low BMD (T-score ≤ -1.5 and > -3.0)	Lumbar spine BMD at 12 months compared to placebo	Completion of trial expected in March 2011
III	39	NCT00529373	50 mg weekly	16,716	Postmenopausal women ≥ 65 years with osteoporosis	Morphometric vertebral fractures, hip fractures and clinical nonvertebral fractures (time frame: duration of treatment)	Completion of trial expected in July 2012

BMD, bone mineral density.

compared to baseline, as well as changes in bone turnover markers. After 24 months of treatment, there was a progressive dose-related increase in BMD with the dose of 50 mg weekly of odanacatib, resulting in a 5.5% increase at the lumbar spine and 3.2% increase at the total hip. The urine NTX/Cr decreased by 52%, while the BSAP decreased by 13% with the dose of 50 mg.

Phase III clinical trials

A randomized, double-blind, placebo-controlled, parallel-assignment phase III study (NCT00729183) to evaluate the efficacy and safety of weekly oral odanacatib 50 mg in postmenopausal women with low BMD is fully enrolled (N = 180) and ongoing (49). The primary endpoint in this study is the percent change in lumbar spine BMD at 24 months compared to baseline; other endpoints include novel imaging endpoints, as determined by quantitative computer tomography (QCT) and extreme CT.

A very large, fully enrolled (N = 16,716), randomized, double-blind, placebo-controlled phase III clinical trial of weekly oral odanacatib 50 mg in women aged 65 years and older with postmenopausal osteoporosis (with or without prior vertebral fractures) is ongoing (NCT00529373) (50). The primary endpoint is the cumulative incidence of radiographic spine fractures and fractures at the hip and other skeletal sites compared with placebo. The expected study completion date is July 2012. This is the pivotal trial designed to assess the efficacy of odanacatib for reducing fracture risk. Demonstration of vertebral fracture risk reduction is required for regulatory approval as a therapeutic agent for the treatment of postmenopausal osteoporosis.

Another fully enrolled (N = 160) phase III trial is evaluating the effect of weekly oral odanacatib 50 mg on BMD and bone turnover markers in postmenopausal women aged 60 years and older previously treated with alendronate (NCT00885170) (51). The primary endpoint is percent change in BMD from baseline at the femoral neck at 24 months. The expected completion date is September 2011.

A study of odanacatib in men aged 40-95 years with osteoporosis (NCT01120600) has a start date of July 2010 and expected completion date of May 2014, with a target enrollment of 250 subjects (52). The primary endpoint of this study is the percent change in BMD at the lumbar spine at 24 months.

Safety

In two reported phase I clinical trials with daily and weekly dosing of odanacatib, adverse experiences with odanacatib and placebo were well matched and transient (5). No clinically significant abnormalities were reported for routine chemistry, complete blood count, urinalysis, electrocardiogram, physical examination and vital signs. There were no serious adverse events and no discontinuations due to clinical or laboratory adverse events.

The phase II dose-ranging study with odanacatib reported a generally favorable safety profile, with no dose-related trends for any adverse events (47, 48). All 399 randomized subjects were included in the 12-month safety analysis. The overall incidences of clinical laboratory adverse events, discontinuations due to adverse events, serious adverse events and adverse events thought by blinded investigators to be drug-related were similar in all treatment groups. All

320 women who entered the 7-year extension were included in the 24-month safety analysis. Treatment did not result in any clinically important changes in calcium or mineral homeostasis. Clinical adverse events were similar in all treatment groups compared with placebo. There was no pattern of treatment related intolerance through 24 months. Because of dermatological and pulmonary adverse events reported with another cathepsin K inhibitor (44), particular attention was directed toward similar issues with odanacatib. The most common skin-related adverse events were rashes. Over 2 years of treatment, rash was reported in 4.8% of subjects receiving the dose of 50 mg weekly of odanacatib and in 7.9% of those receiving placebo (48). There were 9 patients with rash in the placebo group and 7, 5, 6 and 6 patients with rash, respectively, in the 3-, 10-, 25- and 50-mg odanacatib groups (47). With regard to upper respiratory tract infections, there was no evidence of a pattern with regard to time of onset, duration of symptoms, diagnosis or dose-response across treatment groups.

Double fluorochrome-labeled transiliac bone biopsies were obtained in 32 study subjects at 12 investigative sites near the end of the second year of treatment in the phase II study (47). Of these biopsies, 28 were of sufficiently good quality for evaluation of bone histomorphometry. Qualitative assessment revealed no apparent abnormalities. Giant osteoclasts were not seen. There were no clinically important differences among treatment groups for activation frequency, bone formation rate or osteoclast surface/bone surface ratio. Due to the small sample size, the statistical significance of small differences in measured parameters could not be determined.

CONCLUSIONS

Cathepsin K has emerged as a valid target for therapeutic intervention in the management of patients with osteoporosis and other skeletal disorders associated with high bone turnover. The development of cathepsin K inhibitors has been challenged by difficulties in achieving a desirable level of antiresorptive effect and specificity for cathepsin K, with particular concern regarding possible adverse nonskeletal effects on tissues such as skin and lungs. Odanacatib has been shown to have robust, sustained and reversible antiresorptive activity, while having no demonstrable effect on off-target cathepsins as compared with balicatib and relacatib. The preliminary finding of less suppression of bone formation markers than bone resorption markers is intriguing and suggests the possibility that this may be a "formation-sparing" antiresorptive agent. If this phenomenon is sustained with long-term use, it may represent a partial uncoupling of bone resorption and formation, with potentially important therapeutic implications. This would suggest a possible extension of the "window" of effectiveness for increasing BMD beyond the time of the BMD plateau that is typically observed with bisphosphonates. Mechanistically, this may be the result of continued molecular signaling from osteoclasts to osteoblasts with odanacatib therapy, while with bisphosphonates there may be a more profound reduction or total cessation of such signaling. The phase II dose-ranging trial showed an increase in BMD that warrants further investigation for antifracture efficacy. It is not yet known whether odanacatib reduces fracture risk or has clinical advantages over currently available therapeutic options.

DISCLOSURES

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