



DRUG PROFILE

Odanacatib, a cathepsin K inhibitor for the treatment of osteoporosis and other skeletal disorders associated with excessive bone remodeling

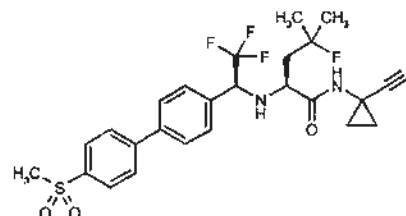
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Odanacatib (MK-0822, MK-822) is an orally administered cathepsin K inhibitor being developed by Merck & Co Inc, under license from Celera Group, for the treatment of osteoporosis and bone metastases. Cathepsin K, a lysosomal cysteine protease that is expressed by osteoclasts during the process of bone resorption, acts as the major collagenase responsible for the degradation of the organic bone matrix during the bone remodeling process. Because excessive bone remodeling is a key element in the pathogenesis of postmenopausal osteoporosis and other skeletal disorders, cathepsin K is a potential target for therapeutic intervention. In a phase II clinical trial, weekly doses of odanacatib increased bone mineral density (BMD) and reduced bone turnover markers in postmenopausal women with low BMD. No tolerability concerns or evidence of skeletal toxicity were reported. Phase III trials, including a trial to evaluate the effects of odanacatib on fracture risk in up to 20,000 women with postmenopausal osteoporosis, were ongoing or recruiting participants at the time of publication. Odanacatib is a promising agent for the management of postmenopausal osteoporosis and other skeletal disorders associated with excessive bone remodeling.

Introduction

Osteoporosis is a common skeletal disease characterized by low bone mineral density (BMD) and poor bone quality that reduces bone strength and increases the risk of fractures [506066]. In 2000, an estimated 9.0 million osteoporotic fractures occurred worldwide, of which 1.6 million were hip fractures, 1.7 million were forearm fractures and 1.4 million were clinical vertebral fractures [1047831]. Overall, 61% of all osteoporotic fractures and 70% of hip fractures occurred in women. The greatest number of fractures was observed in Europe (34.8%), followed by in the Western Pacific region, Southeast Asia and the Americas. Together, Europe and the Americas accounted for 51% of the global burden of osteoporotic fractures [1047831]. The consequences of fractures include long-term disability, loss of independence and death [1026402], [1026406]. The economic toll (mostly associated with hip fractures) is high, with direct healthcare expenditures that were estimated to be approximately US \$17 billion in the US in 2005 [936047] and €32 billion (US \$36 billion) in Europe in 2000 [1026414]. BMD testing can diagnose osteoporosis before the first fracture occurs [1026415], [1043673], and can identify patients who are likely to benefit from therapy [1026437]. When the indication of treatment is unclear or when BMD testing is unavailable, country-specific cost-utility analyses can be combined with a fracture risk assessment algorithm to determine a fracture risk threshold at which initiating drug therapy is cost-effective [1026437].

Therapeutic Odanacatib**Originator** Celera Group**Licensee** Merck & Co Inc**Status** Phase III Clinical**Indications** Bone metastases, Postmenopausal osteoporosis**Actions** Anticancer, Anti-inflammatory, Bone resorption inhibitor, Cathepsin K inhibitor**Technology** Oral formulation**Synonyms** MK-0822, MK-822

Although many currently available drugs have been demonstrated to reduce fracture risk [1026439], patients who could benefit from taking such drugs are often not recognized as being at risk for fracture and are not prescribed treatment [1026440]. Of the patients who

are treated, many do not follow a treatment schedule correctly or for a sufficient length of time to achieve the desired reduction in fracture risk [1026442], [1026444]. Oral bisphosphonates – the drugs most commonly used to treat osteoporosis – must be administered in a complex manner. As a consequence of the poor gastrointestinal absorption (~ 0.6%) of bisphosphonates [1045720], the medication must be swallowed with water on an empty stomach after an overnight fast, followed by a post-dose fast of 30 to 60 min; in order, to reduce the risk of esophageal irritation because of reflux of the medication, the patient must also remain upright for at least 30 to 60 min after dosing [1045737]. Patients may fail to start or continue treatment because of concerns such as drug cost, side effects or fear of side effects.

Drugs that are approved for the prevention and/or treatment of osteoporosis in the US include oral bisphosphonates (eg, alendronic acid, risedronate sodium and ibandronic acid), injectable bisphosphonates (eg, ibandronic acid and zoledronic acid), an estrogen agonist/antagonist (raloxifene), salmon calcitonin, estrogen and a bone anabolic drug (teriparatide). Drugs approved in other countries also include strontium ranelate, tibolone, lasofoxifene, bazedoxifene and recombinant human parathyroid hormone₍₁₋₈₄₎. Efforts to improve the treatment of osteoporosis and reduce the burden of osteoporotic fractures have included the development of drugs with longer dosing intervals, extending as long as 1 or 2 years with zoledronic acid for the treatment and prevention of osteoporosis, respectively, and methods of administration that may provide improved patient acceptance (eg, injectable ibandronic acid or zoledronic acid). As a better understanding of the molecular regulators of bone remodeling has evolved, new targets for therapeutic intervention have been identified [1026447], creating the possibility of developing treatments with improved risk/benefit profiles.

Bone remodeling is the dynamic process by which the adult skeleton is continually broken down and reformed through the coordinated activity of osteoclasts (bone-resorbing cells) and osteoblasts (bone-forming cells) acting in discrete packets on the surface of trabecular bone and in Haversian systems of cortical bone [674252]. When bone resorption and formation are well balanced, BMD remains stable. When bone resorption exceeds bone formation, as observed in postmenopausal estrogen-deficient women, there is a net loss of bone and, with time, osteoporosis results [1026451]. RANKL (receptor activator of NF κ B ligand) is the principal regulator of osteoclastic bone resorption [575538]. When RANKL binds to RANK on osteoclasts and pre-osteoclasts, there is an increase in osteoclast formation, activity and survival, resulting in increased bone resorption [1045358]. Osteoprotegerin (OPG) is a naturally occurring soluble non-signaling 'decoy receptor' that binds to RANKL, preventing the interaction of the ligand with RANK, and thereby inhibiting osteoclastogenesis and downregulating bone resorption [309211]. Denosumab (Amgen Inc/Daiichi Sankyo Co Ltd/

GlaxoSmithKline plc) is a fully human mAb to RANKL that acts in a similar manner to OPG. A phase III clinical trial demonstrated that denosumab reduced the risk of vertebral fractures, non-vertebral fractures and hip fractures in postmenopausal women with osteoporosis [1033443], suggesting that the compound may be a potential future treatment for osteoporosis and other skeletal diseases that are associated with high levels of bone resorption.

Osteoclastic bone resorption requires the attachment of an osteoclast to the bone surface by means of a 'sealing zone' to create a self-contained compartment between the bone surface and the ruffled border of the osteoclast [1043666]. Subsequently, the establishment of an acidic microenvironment demineralizes the bone, with degradation of the organic bone matrix occurring through the action of cysteine proteases [1026457]. Cathepsin K, the most abundant cysteine protease expressed in osteoclasts, is a rate-limiting factor for osteoclastic bone resorption [1016538]. Cathepsin K knockout mice exhibit increased BMD; thickened bone trabeculae and increased bone strength compared with wild-type mice [1026471]. Cathepsin K also acts as the major collagenase responsible for the degradation of the organic bone matrix during the bone remodeling process [1026457]. Furthermore, cathepsin K is expressed by other cells, including synovial fibroblasts and macrophages in rheumatoid arthritic joints, and tumor cells in breast and prostate cancer [1026480], [1045368]. Thus, cathepsin K has been identified as a potential target for therapeutic intervention in the treatment of osteoporosis and other skeletal disorders associated with high levels of bone turnover [1026474].

Osteoblastic bone formation is upregulated by molecules such as bone morphogenetic proteins [1026475], insulin-like growth factor 1 [1026476] and Wnt (a family of proteins involved in intracellular signaling that are secreted by many cell types [1026477]), and is downregulated by other naturally occurring extracellular proteins such as sclerostin and dickkopf [933011]. The modulation of the production or activity of such proteins may have therapeutic applications, and therefore are current areas of investigation.

Therapeutic agents for the treatment of postmenopausal osteoporosis act by correcting the imbalance between bone resorption and formation. Antiresorptive drugs (eg, bisphosphonates, raloxifene and salmon calcitonin) function primarily by reducing bone resorption [1045375], whereas drugs that are anabolic for bone (eg, teriparatide) function primarily by increasing bone formation [933011]. However, because bone resorption and formation are closely coordinated through 'cross-talk' between osteoclasts and osteoblasts, the changes in resorption and formation usually occur concurrently [1026478]. For example, bisphosphonates not only suppress bone resorption, but ultimately also decrease bone formation [1045375], and teriparatide not only stimulates bone

formation, but eventually also increases bone resorption [933011]. The 'coupling' of bone resorption and formation is a limiting factor in achieving the goal of fully restoring bone strength and bone quality in patients with osteoporosis. Once the therapeutic window of bone formation exceeding bone resorption is passed, there may be little additional benefit to further therapy, although the continued suppression of excessive bone turnover with drug therapy may still be desirable. An agent that results in the prolonged 'uncoupling' of bone resorption and formation, stimulating formation more than resorption or suppressing formation less than resorption, may have potential advantages compared with currently available drugs. Strontium ranelate, approved for the treatment of postmenopausal osteoporosis in many countries (not including the US), has been suggested to be effective in part because of the modest uncoupling of resorption and formation [581706]. Some combinations of drugs, such as teriparatide and raloxifene, may also result in at least a transient prolongation of the therapeutic window in which bone formation exceeds resorption [940262].

Inhibitors of cathepsin K exert an antiresorptive effect that could be beneficial in the treatment of postmenopausal osteoporosis and bone loss associated with other skeletal diseases [1026480]. The design of an optimal cathepsin K inhibitor remains in progress. Balicatib, relacatib and MIV-701 were all discontinued after reaching clinical trials because of adverse reactions or because of inferior pharmacokinetics or efficacy compared with newer agents under development [747221], [839436], [1026481], [1038636]. Odanacatib from Merck & Co Inc, under license from Celera Group, is an investigational antiresorptive drug that targets cathepsin K. Of the aforementioned agents, odanacatib appears to be the most selective for cathepsin K, whereas balicatib and relacatib have a comparatively greater effect on other cathepsins (eg, cathepsins B, L and S) [890810]. There is also evidence that the suppression of bone formation may occur to a lesser degree than the suppression of bone resorption with odanacatib, with the trajectory of bone density increase appearing to be relatively linear during the first 2 to 3 years of treatment [1016552], [1042385], suggesting the possibility of lengthening the window of therapeutic effect beyond that available with current drugs. This drug profile reviews the evidence supporting the ongoing development of odanacatib as a potential treatment for postmenopausal osteoporosis and other skeletal disorders associated with excessive bone remodeling. At the time of publication, odanacatib had reached phase III trials for the treatment of postmenopausal osteoporosis (ClinicalTrials.gov identifiers: NCT00729183, NCT00529373 and NCT00885170), and was also undergoing phase II trials for the treatment of bone metastases [757430].

Synthesis and SAR

The early development of cathepsin K inhibitors focused on carbonyl-containing, transition state mimic-based inhibitors, such as peptide aldehydes [303711], aminomethyl ketones [406954] and hydroxymethyl ketones [1026486]. The more

recent use of nitrile-based inhibitors, as exemplified by tri-ring benzamide moieties with an aminocyclohexanecarboxylate residue at P2, yielded potent, selective, orally effective inhibitors of cathepsin K [1026487]. In an evaluation of the *in vitro* activity of analogs of L-873724 (Merck & Co) with P1 substitutions and stabilized P2 groups, the optimal combination of potency and selectivity was observed with the 4-fluoro-leucine derivative odanacatib [890810]. The compound had little selectivity for cathepsin L, a protease that has been associated with cardiomyopathy in cathepsin L knockout mice [1026489].

Odanacatib, a [2,2,2-trifluoro-1-(biphenyl-4-yl)ethyl]-4-fluoro-leucine derivative of 4-fluoro-leucine, was prepared in six steps from commercially available 1-(4-bromophenyl)-2,2,2-trifluoroethanone, with high enantioselectivity and without the need for chromatography [1016540]. The key step was the stereospecific S_N2 triflate displacement of (1R)-1-(4-bromophenyl)-2,2,2-trifluoroethyl trifluoromethanesulfonate with (S)- γ -fluoro-leucine ethyl ester in 95% yield and without the loss of any enantiomeric excess. The starting trifluoroacetophenone in toluene was reduced with catechol borane in the presence of (S)-butyloxazaborolidine catalyst at -70°C to room temperature to produce the corresponding (R)-alcohol in 96% yield and 92% enantiomeric excess. The alcohol was converted to the corresponding triflate using standard procedures, mixed with ethyl 4-fluoro-L-leucinate and potassium carbonate in cyclohexane at 65 to 70°C and aged for 24 h, resulting in ethyl (S)-2-[(S)-1-(4-bromo-phenyl)-2,2,2-trifluoro-ethylamino]-4-fluoro-4-methyl-pentanoate (95% yield; 84% diastereoisomeric excess). Palladium-catalyzed Suzuki cross-coupling of the crude bromophenyl ester with 4-methylsulfonylphenylboronic acid under standard conditions yielded the corresponding biphenyl ester derivative. The crude ester was hydrolyzed with lithium hydroxide monohydrate at 30 to 35°C . The resultant acid in dimethyl acetamide at 3°C was treated with 1-amino-cyclopropanecarbonitrile and *O*-(7-azabenzotriazol-1-yl)-*N,N,N'*-tetramethyluronium hexafluorophosphate, followed by ethyldiisopropylamine to produce odanacatib (79% yield; 98.5% diastereoisomeric excess). The overall yield for the six-step synthesis was 61% [1016540].

Another synthesis describes the use of a readily available aspartic acid derivative that was prepared via the following consecutive steps: (i) reduction to form a cyclic carbamate; (ii) addition of methylmagnesium bromide; (iii) fluorination; (iv) conversion to a trifluoromethylaldimine derivative; (v) stereoselective addition of bromophenyllithium; (vi) Suzuki coupling; and (vii) amidation [890810], [WO-2003075836]. Similar procedures and preparation of various intermediates are also described in WO-2006017455, WO-2008119176 and WO-2006034004.

Preclinical development

In vitro

In an *in vitro* functional bone resorption assay, odanacatib inhibited human cathepsin K with an IC_{50} value of 0.20 nM (3- to 4-fold more potently than balicatib and relacatib),

and was at least 300-fold more selective for cathepsin K compared with other known human cathepsins [890810], [913127].

Another study evaluated the cellular effects of odanacatib in blocking bone resorption [1016546]. The localization of cathepsin K in osteoclasts was confirmed using electron microscopy immunolabeling in thin sections of mouse femur. Cathepsin K was observed within lysosomes, late endosomes, ruffled border and resorption lacunae, but not in osteoblasts or other bone marrow cells. In human osteoclasts cultured on dentin or plastic, odanacatib (100 nM) demonstrated no effect on the levels of multinucleated tartrate-resistant acid phosphatase 5b (TRAP5b; an exploratory marker of osteoclast number); in contrast, treatment with alendronic acid (5 μ M) resulted in reduced levels of TRAP5b [1016546]. While confocal microscopy with an anti-cathepsin K antibody confirmed expression of the protease in all osteoclasts on bone, a fluorescence probe of an analog of odanacatib detected active enzyme in only a subgroup of resorbing cells, with cathepsin K being localized to intracellular vesicles and ruffled border. These data suggested that the mechanism for odanacatib-mediated inhibition of osteoclastic bone resorption involved a reduction of matrix degradation without affecting osteoclast formation, survival or polarization [1016546].

In vivo

Odanacatib was evaluated in a 21-month study of adult female rhesus monkeys (aged 13 to 19 years) that were randomly assigned to one of four treatment groups: intact (non-ovariectomized) plus vehicle, ovariectomized (OVX) plus vehicle, or OVX plus odanacatib (6 or 30 mg/kg/day po) [913148], [1016545], [1016547], [1016550], [1016551], [1042643], [1042644], [1042645], [1042646]. BMD and bone turnover biomarkers were measured every 3 months, with biomechanical bone strength testing (three-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. Final spine (11 and 17% increases in the 3- and 6-mg/kg odanacatib groups, respectively), total hip (10 and 16%) and femoral neck (11 and 12%) BMDs were higher in the odanacatib-treated groups compared with the OVX-vehicle group [1016547], [1016550]. Bone resorption biomarkers, including cross-linked N-terminal telopeptide of type I collagen (NTx), cross-linked C-terminal telopeptide of type I collagen (CTx) and deoxypyridinoline (DPD); and bone formation biomarkers including N-terminal propeptide of type I collagen (P1NP) and bone-specific alkaline phosphatase (BSAP), were measured in the urine or serum [1016551]. By week 6, the levels of NTx, CTx and DPD in OVX monkeys had increased from baseline by 60, 100 and 80%, respectively; by week 15, P1NP and BSAP peaked at 267 and 75% greater than baseline levels, respectively.

By week 72, bone resorption and the formation biomarkers in the odanacatib-treated groups were dose-dependently suppressed to levels equal or less than that of the intact animals. Odanacatib did not suppress TRAP5b, consistent with the novel mechanism of antiresorptive action [1016551].

Peripheral quantitative computed tomography was used to assess *in vivo* macro- and microarchitectural parameters of bone strength in the monkeys [1016545]. Treatment with odanacatib preserved cortical thickness, which remained significantly greater at the distal radius and tibia compared with the OVX-vehicle group. A trend toward thicker trabeculae and higher volumetric BMD was also reported for the odanacatib-treated animals [1016545]. High-resolution finite element analysis and 3D bone morphology was used to estimate bone strength *in vivo*, and was validated by the direct measurement of bone strength using biomechanical testing of the excised distal radius of sacrificed animals at the end of the study [1042646]. Biomechanical axial compression demonstrated that the bone of odanacatib-treated animals was 39% stronger than the bone of OVX-vehicle-treated animals ($p = 0.0018$) [1042646]. A further measure of bone strength parameters revealed that the mid-point femur ultimate load was 25 and 32% greater in the low- and high-dose odanacatib-treated groups than in the OVX-vehicle group, respectively ($p = 0.002$); in addition, mid-point femur stiffness was increased by 23 and 33% compared with that of the OVX-vehicle group ($p = 0.009$) [1016550]. Normal bone quality was maintained; double tetracycline-labeled bone biopsies at the end of study demonstrated that the histomorphometric parameters of bone formation in trabecular regions was unaffected by odanacatib treatment [1016547], [1016550], suggesting that, unlike bisphosphonates, odanacatib displays a bone formation-sparing antiresorptive effect [1042645]. Additional histomorphometric analyses of the femoral neck supported the hypothesis that odanacatib can inhibit trabecular bone remodeling while building cortical bone, in part by stimulating periosteal bone formation [1042643]. A dose-dependent effect of odanacatib was observed on the rate of periosteal femoral neck bone formation, with a 1.5-fold increase in the long-term mineral apposition rate observed in the high-dose odanacatib group compared with the OVX-vehicle group [1042643].

In a 28-week study of adult female New Zealand white rabbits (aged 7 months), animals were randomized to one of five groups: sham OVX plus control diet, OVX plus control diet, OVX plus 0.0016% of odanacatib diet, OVX plus 0.004% of odanacatib diet, or OVX plus control diet with alendronic acid (0.3 mg/kg sc, twice weekly) [1016548]. Assessments included BMD and double tetracycline-labeled bone histomorphometry at necropsy. In the OVX-control animals, the decline from baseline BMD in lumbar vertebra L3 was 8.7% ($p < 0.05$), while bone loss was prevented in both the odanacatib-treated groups and the alendronic acid-treated group. Bone histomorphometry revealed that the mineralizing surface

(a measure of bone formation) was similar or higher for the odanacatib-treated groups (9.5 and 15.0% with 0.0016 and 0.004% of odanacatib, respectively) compared with the OVX-control group (10.0%), while the mineralizing surface for the alendronic acid group was lower (5.5%). These data suggested that the odanacatib-related prevention of bone loss in estrogen-deficient rabbits did not suppress bone formation, whereas treatment with alendronic acid was associated with the inhibition of bone formation [1016548].

Toxicity

Extensive studies of odanacatib in adult female rhesus monkeys reported no evidence of adverse skeletal effects, as assessed by bone histomorphometry and bone strength testing [1016550].

Metabolism and pharmacokinetics

Odanacatib demonstrated excellent metabolic stability in hepatocyte incubations in several animal species [890810]. In standard incubations, 96 and 98% recovery of the parent compound was observed in rat and rhesus monkey hepatocytes, respectively. In both dog and human hepatocyte incubations, recovery was > 99% [890810].

The pharmacokinetics of odanacatib were evaluated in preclinical studies in rats (10 mg/kg po), dogs (5 mg/kg po) and rhesus monkeys (5 mg/kg po) [890810]. Oral bioavailability was demonstrated to be highly dependent on vehicle, dosage and sample preparation. In dogs, the oral bioavailability of odanacatib was 6% when dosed as a suspension in 0.5% methocel, but 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 clearance and volume of distribution at steady state for odanacatib in rats, dogs and monkeys were 2.0, 0.1 and 6.1 ml/min/kg and 1.1, 0.6 and 1.6 l/kg, respectively. The $t_{1/2}$ values were of long duration in all species (6, 57 and 18 h in rats, dogs and rhesus monkeys, respectively), consistent with the observation of metabolic stability [890810].

Data from two phase I clinical trials in healthy postmenopausal women reported a serum $t_{1/2}$ value for odanacatib that ranged from approximately 66 to 93 h with once-weekly (5 to 100 mg po, for 3 weeks) or once-daily (0.5 to 10 mg po, for 3 weeks) dosing [1016538]. Weekly dosing was associated with a moderate serum 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 observed during the dosing interval. Trough concentration ($C_{168\text{ h}}$) data suggested that steady state conditions were achieved in the third week of dosing with both regimens. The pharmacokinetic profiles typically demonstrated a primary peak with a T_{max} value of approximately 4 to 6 h, and a secondary peak often observed at approximately 24 h (more notably with the

weekly dosing regimen). On both the first and last days of dosing, the AUC, C_{max} and $C_{168\text{ h}}$ values increased approximately dose proportionally from 0.5 to 10 mg, but less than dose proportionally at doses \geq 25 mg [1016538].

Two phase I, double-blind, randomized, placebo-controlled, single-dose clinical trials investigated the pharmacokinetics and tolerability of odanacatib (up to 600 mg po) with or without food (NCT00863590; MK0822-001) in healthy volunteers ($n = 24$), and the effects of the drug with a light breakfast (NCT00863525; MK0822-006) in healthy male volunteers ($n = 8$). The administration of odanacatib with food increased the bioavailability of the drug by 30 to 100% depending on meal type used [969430].

Clinical development

Phase I

Two phase I, randomized, double-blind, placebo-controlled, 3-week clinical trials of odanacatib have been reported [913132], [1016538]. One trial (NCT00770159; MK0822-005) investigated once-weekly odanacatib dosing (5, 25, 50 or 100 mg po) in healthy postmenopausal women ($n = 49$) aged \leq 75 years, and the other trial (NCT00769418; MK0822-002) evaluated once-daily dosing (0.5, 2.5 or 10 mg po) in healthy postmenopausal women ($n = 30$) aged \leq 70 years. At the three highest doses, weekly odanacatib resulted in substantial reductions of approximately 62% (at $C_{168\text{ h}}$) from baseline in the levels of two biochemical markers of bone resorption, serum CTx and urinary NTx normalized to creatinine (NTx/Cr); these reductions were sustained during the dosing interval. At the two highest doses, daily odanacatib resulted in significant reductions from baseline in CTx and NTx/Cr (up to 81% reductions from baseline for each marker) beginning 3 to 5 days after the initiation of treatment and continuing until day 24. The 5-mg weekly dose and the 0.5-mg daily dose resulted in only slight reductions in bone resorption markers; no significant changes were observed in the levels of TRAP5b or the two bone formation biomarkers serum BSAP and serum osteocalcin [913132], [1016538].

Phase II

A phase II, randomized, double-blind, placebo-controlled, dose-ranging clinical trial (NCT00112437; MK0822-004) evaluated the effects of weekly odanacatib (3, 10, 25 or 50 mg po) for up to 2 years in postmenopausal women (average age of 64.2 years) with low BMD (baseline BMD T-score [a measure of the departure of the BMD value of a patient from the mean BMD value of a population of healthy young adults in units of the population standard deviation] of \leq -2.0 at the lumbar spine, femoral neck, trochanter or total hip and \geq -3.5 at all other skeletal sites measured) [913122], [913123], [943973], [1006480], [1016552], [1016553], [1020363], [1041779], [1041798]. A total of 399 women were enrolled in the trial, with 280 women completing the full 2 years of treatment. After 2 years of treatment, a progressive, dose-related increase in BMD from baseline was observed. The 3-mg dose did not have a therapeutic effect, with BMD decreasing at the lumbar spine, total hip and femoral neck [943973]. At the 50-mg dose, lumbar spine and total hip

BMD increased by 5.5 and 3.2% from baseline levels, respectively, compared with -0.2 and -0.9%, respectively, for placebo (both $p \leq 0.001$). At the same sites, a smaller, but still significant ($p < 0.05$), increase in BMD was observed with the 10- and 25-mg doses of odanacatib. At a dose of 50 mg, treatment resulted in decreases from baseline of 31 and 52% (both $p \leq 0.001$) in the levels of serum CTx and urinary NTx/Cr, respectively; changes from baseline with placebo were -5 and 33%, respectively. Serum BSAP and P1NP decreased from baseline by 13% ($p = 0.002$) and 20% ($p = 0.011$), respectively, compared with a decrease of 5% and an increase of 3% observed with placebo [1016552]. In preliminary data from 27 participants, transilial biopsies demonstrated no significant effect on bone remodeling after 2 years of treatment with odanacatib [1006480], [1020363], [1041779].

A 1-year extension of the phase II clinical trial assessed the efficacy and long-term safety of odanacatib and the effects of discontinuing therapy [1041567], [1042385]. After 2 years, the remaining participants were re-randomized to doses of 50 mg (po) once-weekly or placebo. A total of 189 women continued in the extension trial, with 169 participants completing 3 years of therapy. Continued treatment with 50 mg of odanacatib for 3 years ($n = 20$) produced significant increases from baseline in lumbar spine (7.8%), total hip (5.8%), femoral neck (5.0%) and trochanter (7.4%) BMD. Minimal change was observed in total body BMD (-0.4%) with continued treatment of 50 mg of odanacatib for 3 years. Serum CTx remained suppressed at month 36 (-24%), but levels of both BSAP and P1NP increased, and were relatively unchanged from baseline at month 36. The discontinuation of odanacatib therapy resulted in bone loss at all sites, with higher rates observed in the initial 6 months and less bone loss occurring between months 30 and 36. At the end of 3 years, the mean BMD among participants who received 50 mg of odanacatib for 2 years and placebo in the third year ($n = 18$) was significantly higher than baseline for femoral neck, was non-significantly higher than baseline for spine, and did not differ from placebo for total hip and trochanter BMD. Furthermore, the discontinuation of odanacatib led to a rapid increase of higher-than-baseline values in biochemical markers of bone remodeling. The rebound in bone turnover occurred promptly after treatment discontinuation, and was largely resolved with time. For example, mean serum CTx reached > 2-fold the baseline level by month 30, but was approximately 10% higher than baseline by month 36 [1041567], [1042385].

A phase II, randomized, double-blind, active-control clinical trial (NCT00399802; MK0822-016) investigated odanacatib (5 mg po qd, for 4 weeks) in patients ($n = 43$; average age of 60 years) with breast cancer and metastatic bone disease [969432], [969441], [1016544]. The mean change from baseline in urinary NTx and DPD at 4 weeks in patients receiving odanacatib was -77 and -30%, respectively, compared with -72 and -52% in patients

receiving single-dose zoledronic acid (4 mg iv). Odanacatib exhibited minimal effect (-9% change from baseline) on bone formation, as measured by serum BSAP [969441].

A phase II, randomized, double-blind, placebo-controlled clinical trial (NCT00242476; 0822A-009) of once-weekly odanacatib (16-week treatment; no dose stated) in elderly (aged ≥ 70 years) male and female participants (expected $n = 216$) with low levels of vitamin D was completed. The primary endpoint was mediolateral body sway at 16 weeks, and the secondary endpoints included safety, tolerability and assessment of functional status using the Short Physical Performance Battery test. No data were available at the time of publication.

A phase II, randomized, double-blind, placebo-controlled clinical trial (NCT00620113; MK0822-022) of once-weekly odanacatib (10, 25 and 50 mg po, for 52 weeks) in patients (expected $n = 280$) with involuntal osteoporosis was ongoing at the time of publication. The primary endpoint was the change in lumbar spine BMD compared with placebo. Secondary endpoints included changes in total hip, femoral neck and trochanter BMD versus placebo. Trial completion was expected in December 2010.

A phase II, randomized, double-blind, placebo-controlled clinical trial (NCT00397683) of odanacatib had been recruiting patients with osteoarthritis of the knee. However, recruitment was suspended in April 2007, and the trial was subsequently terminated by Merck. The reasons for the termination of the trial have not been stated.

Phase III

A phase III, randomized, double-blind, placebo-controlled, parallel-assignment clinical trial (NCT00729183; MK0822-031) to evaluate the efficacy and safety of once-weekly odanacatib (50 mg po) in postmenopausal women with low BMD had completed enrollment (expected $n = 180$) and was ongoing at the time of publication. The primary and secondary endpoints of the trial were the percent changes in lumbar spine BMD at 12 and 24 months compared with baseline; other endpoints included bone microarchitecture. Completion of the trial was expected in May 2011.

A phase III, randomized, double-blind, placebo-controlled clinical trial (NCT00529373; MK0822-018) of once-weekly odanacatib (50 mg po) for up to 3 years was recruiting women (expected $n = 20,000$) with postmenopausal osteoporosis with or without prior vertebral fractures. The primary endpoint of the trial was the cumulative incidence of radiographic spine fractures, and fractures at the hip and other skeletal sites, compared with placebo. The secondary endpoint was the change in BMD during 3 years versus placebo. Completion of the trial was expected in September 2012.

A phase III, randomized, double-blind, placebo-controlled, parallel-assignment clinical trial (NCT00885170; MK0822-042) of once-weekly odanacatib (50 mg po) for

up to 2 years was recruiting postmenopausal women (expected $n = 160$) who were previously treated with alendronic acid. The primary endpoint was the percentage change in BMD from baseline at the femoral neck site. Secondary endpoints included the percentage change in BMD from baseline at the trochanter, total hip, lumbar spine, total body and forearm sites, as well as the effect of treatment on biochemical markers of bone turnover, and on indices of calcium and mineral homeostasis. Completion of the trial was expected in September 2011.

Two additional phase III clinical trials were planned to evaluate the effect of odanacatib in reducing the risk of bone metastasis in women with breast cancer (NCT00692458; MK0822-029) and in men with castration-resistant prostate cancer (NCT00691899; MK0822-030). However, both trials were withdrawn by Merck prior to patient recruitment because of administrative reasons.

Side effects and contraindications

In the two phase I clinical trials of weekly and daily odanacatib dosing in healthy postmenopausal women, adverse events were transient and similar to placebo [1016538]. No clinically significant abnormalities were reported for routine chemistry, complete blood count, urinalysis, ECG, physical examination and vital signs. There were no serious adverse events, and no discontinuations occurred as a consequence of clinical or laboratory adverse events [1016538].

The phase II, dose-ranging clinical trial in postmenopausal women reported a generally favorable safety profile for odanacatib, with no dose-related trends in any adverse experiences [1016552], [1041779]. The number of women with a drug-related adverse event was similar between the 50-mg odanacatib group and the placebo group (34.6 and 39.8%, respectively). The discontinuation rates because of drug-related adverse events were also similar between the two groups (7.7 and 4.8%, respectively). In the 50-mg odanacatib group, the most common drug-related adverse experiences were nausea, headache, rash and muscle spasms [913123], [943973], [1016553], [1041798]. Rash occurred in 4.8% of women receiving 50 mg of odanacatib compared with 7.9% of women receiving placebo [1016552]. There was no dose-dependent increase in the incidence of skin adverse experiences or upper respiratory tract infections during the 2-year trial [943973].

In the 1-year extension trial, the overall incidence of adverse events was similar between the odanacatib and placebo groups, and was similar to the results reported at 2 years [1041567]. The most common clinical adverse experiences (regardless of treatment group) were back pain, arthralgia (joint pain), extremity pain and nasopharyngitis (common cold). Urinary tract infections occurred more frequently in the odanacatib group compared with the placebo group (ten versus one occurrence, respectively); none of the events was classified as drug-related or led to the discontinuation of treatment,

and all were resolved following antibiotic therapy. The incidence of skin disorders in the extension trial was higher in the placebo group than in the odanacatib group (15 versus 12 occurrences, respectively), and discontinuations because of adverse experiences were similar in both groups (four occurrences per group) [1041567].

Patent summary

Odanacatib was first claimed as one of a range of specific cathepsin cysteine protease inhibitors in WO-03075836, which was coassigned to Axys Pharmaceuticals Inc (now Celera South San Francisco [Celera Group]) and Merck Frosst Canada & Co (now Merck & Co Inc). The equivalent US patent, US-07375134, was granted a lifetime extension under US154 until November 2024. The equivalent European (EP-01482924) and Japanese (JP-04201716) patents expire in February 2023.

Merck and Celera have also claimed processes useful for synthesizing cathepsin inhibitors in US-07183425, US-07154005, US-07429674, WO-2006034004 and WO-2008119176. In addition, Merck has filed claims on the use of cathepsin K inhibitors (including odanacatib) for treating obesity (WO-2006076796), atherosclerosis (WO-2006076797) and osteoporosis (WO-2007046842). WO-2008106059 discloses compositions comprising cathepsin K inhibitors (including odanacatib) and excipients for oral and intravenous delivery.

Current opinion

Cathepsin K appears to be a valid target for therapeutic intervention in the management of patients with osteoporosis and other skeletal disorders that are associated with high levels of bone turnover. The development of cathepsin K inhibitors has been hindered by difficulties in achieving a desirable level of antiresorptive effect and specificity for cathepsin K. Odanacatib has exhibited robust, sustained and reversible antiresorptive activity, with no demonstrable effect on off-target cathepsins as observed with balicatib and relacatib.

The effects of balicatib and relacatib on off-target cathepsins may be responsible for the accumulation of undesirable collagen in skin fibroblasts associated with the two compounds [890810]. Phase II clinical development of balicatib was discontinued [747221] because of the occurrence of skin rash and rarer incidences of morphea-like skin reactions [1026481]. To date, odanacatib appears to be well tolerated, with minimal significant adverse events. Shortly after the discontinuation of balicatib, the investigation of relacatib also appears to have been halted, as suggested by the absence of the compound from the GlaxoSmithKline plc pipeline [839436]. Furthermore, MIV-701 was discontinued by Medivir AB [1038636] despite reports of a > 50% reduction in a bone resorption marker in healthy men and postmenopausal women [1026482]. MIV-701 has been superseded by Medivir's next generation of cathepsin K inhibitors, MIV-711 and MIV-710, that demonstrate more favorable efficacy and pharmacokinetics, and have the potential to exploit

additional indications of significant market value, including osteoarthritis, rheumatoid arthritis and metastatic bone disease [1038636].

The most promising of the emerging agents for the treatment of osteoporosis in the near future is denosumab. When used for the treatment of postmenopausal osteoporosis, denosumab is a potent antiresorptive agent with robust fracture-risk reduction, has a good safety profile, requires infrequent dosing (every 6 months) and involves convenient administration (sc injection) [1033443]. While denosumab may be an effective first-line therapy for osteoporosis, the inexpensive generic alendronic acid will likely continue to be the initial drug used for most patients with the disease. When alendronic acid or other oral bisphosphonates cannot be used because of contraindications, gastrointestinal intolerance, malabsorption or poor response to therapy, an injectable bisphosphonate or denosumab (if approved) will be the next tier of therapy. Some patients are also candidates for treatment with a selective estrogen receptor modulator, such as raloxifene or salmon calcitonin. Teriparatide and recombinant human parathyroid hormone₍₁₋₆₄₎ are osteoanabolic agents that are used for patients with a high risk of fracture.

The potential role of odanacatib among other agents remains to be determined. If odanacatib is ultimately demonstrated to have superior anti-fracture efficacy, greater safety or improved tolerability compared with current agents, as well as competitive pricing, then

the compound may become a valuable option in the management of osteoporosis. Of particular interest is the novel mechanism of action of the drug, and the possibility that effects on cortical bone could result in a greater reduction of non-vertebral fractures compared with other antiresorptive agents. At the time of publication, no human fracture data were available for odanacatib.

The preliminary finding that odanacatib suppresses bone formation markers less than bone resorption markers is particularly intriguing, and suggests that the compound may act as a formation-sparing antiresorptive agent. If such action is determined to be sustained with long-term use, odanacatib therapy may represent a partial uncoupling of bone resorption and formation, with important therapeutic implications. By potentially extending the window of effectiveness, BMD may continue to increase for a time period beyond the BMD plateau that is observed with bisphosphonates. Mechanistically, the extended efficacy with odanacatib therapy may be the result of continued molecular signaling from osteoclasts to osteoblasts, while a more profound reduction or total cessation of such signaling may occur with bisphosphonates. The early results from phase II clinical trials of odanacatib demonstrate an increase in BMD that warrants further investigation for anti-fracture efficacy. Whether odanacatib reduces fracture risk, and whether the drug has clinical advantages compared with the currently available options for therapy, remains to be determined.

Deals

Merck & Co Inc

In November 1996, Merck & Co and Celera entered into a collaboration to develop small-molecule inhibitors of cathepsin K, including odanacatib [247587], [310050], [348398], [391631], [433282]. By February 2003, Merck assumed responsibility for further R&D of the compounds [550749]. By September 2007, another milestone payment was made for the advancement of odanacatib into phase III trials [834239].

Development status

Developer	Country	Status	Indication	Date	Reference
Merck & Co Inc	US	Phase III	Postmenopausal osteoporosis	17-SEP-07	943973
Merck & Co Inc	Europe	Phase III	Postmenopausal osteoporosis	17-SEP-07	943973
Merck & Co Inc	Japan	Phase III	Postmenopausal osteoporosis	17-SEP-07	943973
Merck & Co Inc	Mexico	Phase III	Postmenopausal osteoporosis	17-SEP-07	943973
Merck & Co Inc	Russian Federation	Phase III	Postmenopausal osteoporosis	17-SEP-07	943973
Merck & Co Inc	South Africa	Phase III	Postmenopausal osteoporosis	17-SEP-07	943973
Merck & Co Inc	US	Phase II	Bone metastases	30-NOV-06	757430
Merck & Co Inc	South Korea	Discovery	Postmenopausal osteoporosis	25-APR-08	915081
Merck & Co Inc	US	No Development Reported	Osteoarthritis	21-SEP-09	-
Celera Group	US	Discontinued	Osteoporosis	28-FEB-03	550749

Associated patent

Title Cathepsin cysteine protease Inhibitors.

Assignees Merck Frosst Canada & Co [Merck & Co Inc] and Celera South San Francisco [Celera Group]

Publication WO-03075836 18-SEP-03

Inventors Bayly CI, Black C, Leger S, Li CS, McKay D, Mellon C, Gauthier JY, Lau C, Therien M, Truong V-L, Green MJ, Hirschbein BL, Janc JW, Palmer JT, Baskaran C.

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