Denosumab for the Treatment of Osteoporosis

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Abstract

Introduction—Low trauma fractures due to osteoporosis are a major health concern worldwide. Despite the availability of many therapeutic compounds to reduce fracture risk, osteoporosis remains undertreated and the burden of osteoporotic fractures remains high. Denosumab is a novel agent that acts to reduce bone turnover, improve bone mineral density, and reduce fracture risk, offering a favorable efficacy and safety profile.

Areas covered—This review covers the pharmacology and major clinical trials with extension/ post-marketing follow-up, including trials for all FDA-approved indications of denosumab to date.

Expert Opinion—Denosumab is an efficacious and safe osteoporosis treatment option, with current data up to 8 years of continued use showing continued improvement in bone density with sustained fracture risk reduction. Safety profiles overall are similar to placebo, with no new safety concerns in extension trials, though a theoretical increased risk of infection exists with RANKL inhibition. Future considerations include safety of prolonged treatment beyond 8 years, and efficacy/fracture risk after discontinuation or with non-adherence, given the characteristic pharmacodynamic profile of denosumab.

Keywords

denosumab; mAb; osteoporosis; receptor activator of nuclear factor kappa-B ligand; treatment

1. Introduction

In the United States (US), an estimated 54 million individuals are at risk for low trauma fractures associated with osteopenia or osteoporosis, making it a major U.S. public health care concern [1]. Given the projected demographic changes in the USA, it is expected that the current rates of hip and other fractures in men and women > 50 years of age will increase by 50% by 2025 [2]. The clinical sequelae of osteoporotic fractures are significant:

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osteoporotic hip fractures are associated with functional limitations and an excess mortality risk of 15–25% [3], and vertebral fractures are associated with a decreased quality of life, as well as an increase in mortality [4, 5]. Based on the current U.S. National Osteoporosis Foundation guidelines, an estimated 20% of men and 37% of women over age 50 years are potential candidates for treatment to prevent fractures [6].

Although numerous medications are approved for treatment and prevention of osteoporosis, many patients at high risk for fracture are not being treated [7]. Furthermore, when treatment is started, adherence is often poor [8]. There have been concerns about long-term (beyond 3–4 years) efficacy and safety with osteoporosis treatments that may contribute to poor adherence [9].

Denosumab (Box 1) is a novel biologic agent for the treatment of osteoporosis. Up to 8 years of safety and efficacy data are now available from the extension of the pivotal FREEDOM trial, providing longer-term bone density, fracture reduction, and safety/ tolerability data to help guide clinicians in its optimal use in the management of patients at risk for fracture.

2. Overview of the market

Current FDA-approved pharmacological agents for use in osteoporosis and fracture risk reduction include bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid) [10–13], salmon calcitonin [14], estrogen therapy with or without medroxyprogesterone [15, 16], raloxifene [17], conjugated estrogen/bazedoxifene [18], recombinant human parathyroid hormone (1–34) [19], and denosumab [20]. In Europe, strontium ranelate [21] and recombinant human parathyroid hormone (1 – 84) [22] are available for treatment of osteoporosis; however, these agents are not currently FDA-approved for use in the USA. Potential future therapies with novel mechanisms of action that are currently in clinical trials include a cathepsin K inhibitor (odanacatib) [23] and two humanized mAbs to sclerostin (romosozumab, blosozumab) [24,25].

3. Introduction to denosumab

Denosumab is a human monoclonal IgG2 antibody genetically engineered in hamster ovary cells. It has high affinity and specificity for human receptor activator of nuclear factor kappa-B ligand (RANKL), the principle regulator of osteoclastic bone resorption. Denosumab binds to RANKL, preventing RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. This acts to inhibit osteoclast formation, function, and survival, thereby decreasing bone resorption.

4. Pharmacodynamics

In clinical studies reported by the manufacturer using subcutaneous (SC) denosumab 60 mg dosing, C-telopeptide (CTX), a marker of bone resorption, was reduced by 85% at 3 days and below the limit of assay detection in 39% of patients at 1 month in 68% of patients at 3 months. At the end of the 6 month dosing interval, CTX reductions were partially attenuated from maximal reduction of   87% -   45% (range: 45–80%), reflecting some reversibility of

bone remodeling suppression. After discontinuation of denosumab therapy, markers of bone resorption increased to levels 40% – 60% above pretreatment values, but returned to baseline levels within 12 months. Bone formation markers (osteocalcin and procollagen type 1 N-terminal peptide [P1NP]) have been shown to be reduced by 1 month [26].

In a Phase I, dose-escalation clinical study of 49 healthy post-menopausal women given a single dose of denosumab [27] (0.01, 0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg groups, n = 6/group) versus placebo at a 3:1 ratio, decreases in urinary N-telopeptide (NTX, a marker of bone turnover) were observed as early as 12 hours post-dose with mean decrease of 77% in the 3.0 mg/kg group. Of note, the placebo group also showed a decrease of 46% at 12 hours, which was expected due to the diurnal variation of urinary NTX. However, at 24 hours after initial dosing, the mean decrease in urinary NTX was 73% in the 3.0 mg/kg groups versus only 10% in the placebo group. Maximum urinary NTX suppression was noted at 2 weeks for the 0.01, 0.03, 0.3, and 1.0 mg/kg dose groups, 1 month for the 0.1 mg/kg group, and 3 months for the 3.0 mg/kg group (84%). The treatment effect was reversible, with a return to baseline urinary NTX at 2 months for the 0.01 and 0.03 mg/kg dose groups, 4 months for the 0.1 mg/kg group, 6 months for the 0.3 mg/kg group, and 9 months for the 1.0 and 3.0 mg/kg groups, confirming a prolonged antiresorptive effect at higher doses.

In contrast to urinary NTX, bone-specific alkaline phosphatase did not rapidly decrease. A decrease from baseline occurred starting at 2 weeks, with maximum decrease of 53% at 5 months in the 3.0 mg/kg dose group.

The maximum decrease in albumin-adjusted serum calcium observed was 10% (at 14 days in the 0.3 mg/kg group); no subjects had calcium levels below 2 mmol/l. Serum phosphorus levels were also decreased, and serum intact parathyroid hormone (iPTH) levels showed an early, dose-dependent increase. Maximum increase in iPTH was ~ threefold in the 3.0 mg/kg dose group at 4 days post dose, with increases above baseline of 8% and 67% in the 1.0 and 3.0 mg/kg groups respectively at 6 months. Additionally, mean white blood cell count remained stable across all dose groups, with no changes in T and B cell counts (CD3, CD4, CD8, CD20, and CD56) or immunoglobulins. Binding antibodies were not detected.

5. Pharmacokinetics and metabolism

In numerous clinic trials, denosumab has demonstrated dose-dependent, non-linear pharmacokinetics across wide dose ranges, similar to other mAbs. It has a characteristic biochemical profile of prolonged absorption, prolonged β phase, and a more rapid terminal phase [27]. In a study conducted in healthy male and female volunteers (n = 73, age range: 18 to 64 years) following a single SC administered denosumab dose of 60 mg, the mean maximum denosumab concentration (Cmax) was 6.75 mcg/ml (standard deviation [SD] = 1.89 mcg/ml), with a median time to maximum denosumab concentration (Tmax) was 10 days (range: 3 – 21 days), reflecting slow absorption by the SC route. After maximal concentration, serum denosumab concentrations declined over a period of 4 – 5 months with a mean half-life of 25.4 days (SD = 8.5 days; n = 46). No accumulation or change in denosumab pharmacokinetics with time was observed with serial dosing of 60 mg SC every 6 months [26].

A meta-analysis of 7 Phase I studies, 2 Phase II studies, and 2 Phase III studies (n = 1,564) determined the SC bioavailability of denosumab to be 64% with the first-order absorption rate constant $k_a = 0.00883$ per hour, and the RANKL degradation rate was determined to be 0.00148 per hour. It was found that a 60 mg fixed dose of denosumab given every 6 months provided similar RANKL inhibition as using weight-based dosing. Given that the nonlinear pharmacokinetic profile of denosumab is likely caused by RANKL binding, dosing adjustments based on age, gender, race, or body weight are not required [28].

In a study of 55 subjects with renal function ranging from normal to dialysis-dependent, it was concluded that denosumab does not require dose adjustment in patients with renal impairment, as no significant differences were seen in pharmacokinetic or pharmacodynamic parameters in this population [29].

Denosumab has not been evaluated in patients with hepatic impairment. Denosumab pharmacokinetics have not been shown to be affected by the formation of binding antibodies.

6. Clinical efficacy (phase I, II, III studies)

6.1. Phase I study

In a randomized, placebo-controlled, dose escalation study of denosumab in 49 healthy postmenopausal women, subjects were treated with a single SC dose of 0.01, 0.03, 0.1, 0.3, 1.0, or 3.0 mg/kg, or placebo, and monitored for drug safety, tolerability, pharmacokinetics, and effects on bone turnover markers (BTMs). Urinary NTX was suppressed, and a transient decrease in serum calcium (< 10% on average) and a transient increase in serum iPTH (up to threefold after 4 days in the 3.0 mg/kg group) were noted. The treatment was well-tolerated with no drug-related serious adverse events reported [27].

6.2. Phase II study

In a 4-year Phase II randomized, placebo-controlled, dose-ranging study evaluating the efficacy and safety of denosumab in postmenopausal women with low bone mineral density (BMD), subjects were randomized to receive placebo, alendronate, or SC denosumab (q 3–6 months, dose ranges 6 mg-210 mg) for the first 2 years, then re-allocated to continue, discontinue, or discontinue and reinitiate denosumab (60 mg q 6 month dosing); discontinue alendronate; or maintain placebo for 2 more years (n = 262) [30]. Denosumab was effective at increasing BMD (9.4 – 11.8% increase at lumbar spine [LS] compared to 2.4% decrease at LS with placebo after 48 months) and suppressing BTMs in a rapid, sustained manner. Discontinuation of therapy led to return towards baseline values for both BMD (6.4% decrease in BMD 12 months after discontinuation) and BTMs. BTM increases after discontinuation were generally a return to baseline values. BMD and BTM at baseline and 36 months (i.e., 24 months of denosumab and 12 months of discontinuation) were strongly correlated (p < 0.0001).

6.3. Phase III studies

FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months) was a three-year, Phase III clinical trial in 7868 postmenopausal women (age 60–90 years) with osteoporosis (LS or total hip T-score < −2.5 and not <−4.0) who were randomized to receive either SC denosumab 60 mg q 6 months (n = 3902) or placebo (n = 3906) (Table 1) [20]. The primary efficacy endpoint was new vertebral fractures at 36 months. The denosumab group had significant relative risk reduction for vertebral fractures (68%), hip fractures (40%), and non-vertebral fractures (20%) compared with placebo. These data supported FDA approval of denosumab for the treatment of postmenopausal women with osteoporosis at high risk for fracture.

In the FREEDOM extension, which plans to follow patients for up to 10 years of denosumab therapy (7 years of extension beyond the initial FREEDOM trial), results currently are available up to 8 years of therapy (5 years of extension) (Table 1) [31]. At 8 years (1382 long-term, 1296 cross-over subjects from placebo group at year 3), BMD showed continued mean increases from baseline in the denosumab group: 18.5% increase in LS and 8.2% increase in total hip in the long-term group, and 13.8% increase in the LS and 4.8% increase in the total hip in the cross-over group. New vertebral and non-vertebral fracture rate remained low throughout the extension, with a hip fracture rate during year 8 of 0.2% in long-term group and 0.1% in cross-over group.

The FREEDOM extension also addressed the sustainability of anti-fracture efficacy after therapy cessation by following patients who discontinued denosumab in an off-treatment observation period. This subgroup of 797 subjects (470 placebo, 327 denosumab) had completed 2–5 doses of denosumab versus placebo and was followed starting > 7 months after their last dose, for up to 24 months of observation. During the off-treatment period (median 0.8 years per subject), 42% versus 28% of placebo- and denosumab-treated subjects, respectively, initiated other therapy. Following discontinuation, similar percentages of subjects in both groups sustained a new fracture (9% placebo, 7% denosumab) [32].

A subset of the FREEDOM extension cohort included bone histology and histomorphometry evaluation. Transiliac crest bone biopsies in 41 subjected (13 cross-over, 28 long-term therapy) at year 2 of the extension showed normal bone quality, and a subset (n = 15) who were analyzed for dynamic parameters showed low bone turnover [33].

Several studies have compared the bone density response of denosumab to oral bisphosphonates, showing additional benefit with denosumab: DECIDE (Determining Efficacy: Comparison of Initiating Denosumab vs alendronate) [34] and STAND (Study of Transitioning from Alendronate to Denosumab) [35] trials of denosumab versus alendronate (Table 2), and trials of denosumab versus oral risedronate and ibandronate [36,37]. In the DECIDE trial, SC denosumab (60 mg q 6 months) plus weekly oral placebo versus weekly oral alendronate plus SC placebo injections q 6 months were compared over 12 months of use. At 12 months, denosumab showed a significantly greater BMD increase at the total hip compared to alendronate (3.5% denosumab, 2.6% alendronate, p < 0.0001), with treatment difference of 0.6% at femoral neck, and 1.1% at LS. Similar findings were reported with the STAND trial, which investigated denosumab versus alendronate in subjects already being

treated with alendronate. At 12 months, there was a statistically significant greater increase in BMD with denosumab (1.9% increase) compared with continuing alendronate (1.05% increase), p < 0.0001. In a comparison trial of denosumab versus risedronate, postmenopausal women who were previously treated with but suboptimally adherent to alendronate were randomized to receive denosumab SC q 6 months or oral risedronate 150 mg q month for 12 months. After 12 months of therapy, denosumab showed greater BMD gains at total hip (2.0% denosumab, 0.5% risedronate), femoral neck (1.4% denosumab, 0% risedronate), and lumbar spine (3.4% denosumab, 1.1% risedronate), p < 0.0001 at all sites. In a comparison trial of denosumab versus ibandronate, postmenopausal women who were previously treatment with bisphosphonates were randomized to receive denosumab SC q 6 months or oral ibandronate 150 mg q month for 12 months. The results of this trial were similar to the denosumab versus risedronate trial; after 12 months of therapy, denosumab showed greater BMD gains at total hip (2.3% denosumab, 1.1% ibandronate), femoral neck (1.7% denosumab, 0.7% ibandronate), and lumbar spine (4.1% denosumab, 2.0% ibandronate); p < 0.0001 at all sites.

ADAMO (Study to Compare the Efficacy and Safety of DenosumAb Versus Placebo in Males with Osteoporosis) was a randomized controlled trial (RCT) upon which the FDA based its approval for the use of denosumab in the treatment of men with osteoporosis at high risk for fracture. In this study, 242 men ages 30–85 with osteoporosis were randomized to receive denosumab vs. placebo (n = 121 in each group) (Table 1) [38]. The primary endpoint of the study was to assess percentage change from baseline in LS BMD at 12 months. After 12 months, denosumab resulted in BMD increases of 5.7% at the LS, 2.4% at the total hip, and 2.1% at the femoral neck (adjusted p 0.0144 for BMD percent differences at all sites compared with placebo). These results remained robust on further analyses controlling for baseline covariates, such as baseline testosterone levels, BMD T-scores, and 10-year osteoporotic fracture risk.

The Hormone Ablation Bone Loss Trial (HALT) was an RCT of denosumab use in men undergoing androgen-deprivation therapy for non-metastatic, hormone-sensitive prostate cancer resulting in FDA approval for use for that indication (Table 1) [39]. Subjects with prostate cancer on androgen deprivation therapy were randomized to denosumab versus placebo for 24 months (n=734 in each group). The primary end point was the percent change in the baseline BMD of the LS at 24 months. At 24 months, BMD of the LS had increased by 5.6% in the denosumab group as compared with a loss of 1.0% in the placebo group (p < 0.001); significant differences between the two groups were seen at as early as 1 month and sustained through 36 months. Subjects who received denosumab had a decreased incidence of new vertebral fractures at 36 months (1.5%, vs. 3.9% with placebo, relative risk, 0.38; 95% CI, 0.19 – 0.78; p = 0.006).

A 2-year RCT of denosumab was conducted in women with hormone receptor-positive non-metastatic breast cancer treated with adjuvant aromatase inhibitor therapy; this trial led to FDA approval for use to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer (Table 1) [40]. Subjects were randomized to SC denosumab 60 mg q 6 months (n = 127) versus placebo (n = 125), with the primary end point of percentage change in LS BMD from baseline to month 12. LS

BMD increased by 5.5% at 12 months and 7.6% at 24 months greater in the denosumab group versus the placebo group ($p < 0.0001$ at both time points). BMD increases were not influenced by duration of aromatase inhibitor therapy.

DATA (the Denosumab and Teriparatide Administration study) was a 2-year RCT in 94 postmenopausal women with osteoporosis in which subjects were randomized in a 1:1:1 ratio to receive 20 mcg teriparatide daily, 60 mg SC denosumab q 6 months, or both (Table 1) [41]. At 12 months, LS BMD increased more in the combination group (9.1%, [SD 3.9]) than in the teriparatide (6.2% [4.6], $p = 0.0139$) or denosumab (5.5% [3.3], $p = 0.0005$) groups, as did total-hip BMD (combination, 4.9% [2.9]; teriparatide, 0.7% [2.7], $p < 0.0001$; denosumab 2.5% [2.6], $p = 0.0011$). CTX showed maximal suppression in the denosumab and combination groups, and bone formation markers (osteocalcin, P1NP) remained measurable in the combination group in contrast to un-measureable in the denosumab group. These findings are in contrast to studies combining bisphosphonates with teriparatide, which have shown poorer efficacy with combined therapy compared to monotherapy [42,43]. These studies show less suppression of BTMs with combination than with bisphosphonate monotherapy, unlike the DATA trial, which showed maximum suppression of BTMs in both denosumab monotherapy and combination therapy. This effect difference may be due to more effective un-linking of bone resorption and formation with denosumab compared to bisphosphonates; denosumab appears to suppress teriparatide-induced bone resorption while only partially reducing teriparatide-induced bone formation.

The DAPS (Denosumab Adherence Preference Satisfactions) study was a 2-year RCT, which analyzed patient adherence and satisfaction in 221 postmenopausal women with osteoporosis, treated with either denosumab or alendronate in alternating years (Table) [44]. Less non-adherence to therapy was found in the denosumab group versus alendronate (first year, 11.9% vs. 23.4%; second year, 7.5% vs. 36.5%), and 92.4% of subjects expressed preference for denosumab over alendronate.

There are numerous ongoing Phase III trials investigating denosumab use in osteoporosis, including denosumab use for prevention of post-teriparatide bone loss (NCT02166437), denosumab use in glucocorticoid-induced osteoporosis (NCT01465568), denosumab compared with zoledronic acid in women with postmenopausal osteoporosis (NCT01732770), and investigations for use in thalassemia-induced osteoporosis [45] (clinicaltrials.gov).

7. Safety, tolerability, and clinical monitoring

Due to a theoretical risk of impaired immune response and profound decreases of BTMs with RANKL inhibition, the long-term safety profile of denosumab has been carefully scrutinized in ongoing extension trials. With an estimated exposure to denosumab of 1,252,566 patient-years as of September 2013, there have been post-marketing reports of atypical femur fractures (AFF), osteonecrosis of the jaw (ONJ), severe symptomatic hypocalcemia (SSH), and anaphylaxis. Four cases of AFF consistent with American Society for Bone and Mineral Research definitions have been adjudicated; all patients had prior bisphosphonate exposure and suffered AFF within 18 months of exposure to denosumab.

Thirty-two cases of ONJ consistent with American Association of Oral and Maxillofacial Surgeons definitions have been adjudicated. Risk factors for ONJ in this population included use of glucocorticoids/chemotherapy, prior bisphosphonate use, older age, and invasive dental procedures.

Eight cases of SSH were reported including symptoms of seizure and/or tetany; seven of eight of these patients had chronic kidney disease, a known risk factor for hypocalcemia. Anaphylaxis was reported in five patients; there were no fatal outcomes from this complication [46]. Although anaphylaxis and allergic reactions are rare, it would be useful for the manufacturer to provide a test dose of this denosumab.

Significant differences between denosumab treatment and placebo were seen with skin-related conditions in the parent FREEDOM trial (3% denosumab vs 1.7% placebo), with cellulitis as a serious adverse event (AE) more common with denosumab (12 subjects denosumab vs one subject placebo). In the DEFEND (DEnosumab FortifiEs boNe Density) trial (n = 330), the overall incidence of infectious AEs were similar (60% denosumab, 61% placebo); however more serious infections were reported in the denosumab group (eight denosumab, one placebo). These included pneumonia, diverticulitis, appendicitis, sepsis, pyelonephritis, urinary tract infection, and cellulitis in the denosumab group, versus lobar pneumonia in the placebo group [47]. However, in the FREEDOM extension, rates of all, serious, and fatal AEs in the long-term denosumab group were similar to or lower than the parent trial rates. The serious skin infection rate with denosumab was similar to the placebo group (< 0.1/100 subject years in both groups), and the infection rate was lower with denosumab during the extension compared with placebo in the FREEDOM parent study (23.4/100 subject years vs 30.7/100 subject years respectively) [48]. However, an earlier meta-analysis of three Phase II and III studies [49] showed a relative risk of infectious serious AE of 4.45 (95% CI 1.15 – 17.14, p = 0.03) at 24 months of therapy (n = 17 infectious serious AE in combined denosumab arms, n = two infectious serious AE in combined placebo arms). When combined with data from the parent FREEDOM trial, the relative risk of infectious serious AEs decreased to 2.10 (95% CI 0.64 – 6.9, p = 0.22), which was not statistically significant compared to placebo [50]. This meta-analysis also reported no statistically significant increased risk of neoplasm (relative risk 1.11, 95% CI 0.91 – 1.36, p = 0.30), which was an initial concern when denosumab was first marketed. Studies in prevention of skeletal-related events in multiple myeloma have yielded less favorable results, though data is limited [51]. In a Phase III trial comparing denosumab with zoledronic acid in multiple myeloma patients with at least 1 osteolytic lesion, denosumab did not reach superiority (though non-inferiority was achieved), and a post-hoc analysis showed less favorable survival in the denosumab group (HR 2.26, CI 1.13 – 4.50), though AEs were similar between groups [52]. Due to this finding, denosumab is not currently approved for use in multiple myeloma.

The manufacturer of denosumab recommends all patients using denosumab to receive calcium 1000 mg daily and at least 400 IU of vitamin D daily to avoid hypocalcemia complications. Monitoring of calcium, magnesium, and phosphorus in patients with chronic kidney disease is highly recommended. Denosumab is currently contraindicated for use in

those with concurrent hypocalcemia, during pregnancy (category X), and in those with history of hypersensitivity reaction to denosumab [26].

8. Regulatory affairs

The initial U.S. FDA approval for denosumab was in June 2010 for the indication of treatment of osteoporosis in post-menopausal women at high risk for fracture. In September 2011, the FDA granted an additional indication for treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer, and to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. In September 2012, denosumab was approved to increase bone mass in men with osteoporosis at high risk for fracture. The FDA has defined high risk for fracture for both men and women with postmenopausal osteoporosis as a history of osteoporotic fractures, or multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

In addition to FDA approval in the USA, denosumab is currently approved for use in the treatment of osteoporosis in all 27 European Union countries, Canada, and Australia.

9. Conclusion

Denosumab is the first and so far the only RANKL inhibitor approved for treatment of osteoporosis. It is extremely effective at decreasing bone turnover and has reversible effects on discontinuation. Since its approval, it has shown sustained efficacy in increasing BMD and decreasing fracture risk, with extension data now through 8 years of use. Though safety has been a concern for this agent given its novel mechanism, current post-marketing data appear favorable in this aspect, showing good tolerability and safety compared to placebo and bisphosphonates.

10. Expert Opinion

Denosumab is becoming an increasingly utilized therapy in treating osteoporosis and bone density loss in the USA; much of this is due to continued favorable data showing significant efficacy, overall low adverse events, and convenient dosing. The FREEDOM extension has shown no new safety concerns arising in its use up to 8 years. A major benefit of denosumab over the standard therapy with bisphosphonates is a continuous BMD increase with use as opposed to a plateau effect seen with bisphosphonates, and the possibility of combination with teriparatide for further BMD gains.

Although denosumab has some safety concerns, such as AFF and ONJ, in common with bisphosphonates, reassuring characteristics of denosumab include its lack of accumulation in bone and reversibility of antiresorptive effects shortly following the end of the 6 month dosing interval [26, 30]. This rapid "offset" of antiresorptive effect in 6 months contrasts with prolonged persistence of anti-resorption following discontinuation of long-term therapy with commonly used bisphosphonates, particularly alendronate and zoledronic acid. Given the many years of therapy that may be necessary for patients at high risk for fracture, denosumab may prove safer for prolonged periods of use. However, this theoretical safety

benefit has yet to be proven; furthermore, the rapid reversibility of antiresorptive effect with discontinuation of denosumab raises concern of adverse clinical consequences and increased fracture risk in patients who do not return for treatment at regular 6-month intervals. Cessation of denosumab results in an increase of BTMs back to, and transiently above, baseline levels. It is not known whether this time period of accelerated bone turnover is associated with an increase in fracture risk. Non-compliant patients would be at increased risk of this phenomenon, leading to increased need for patient monitoring for adherence. Further, questions remain on how to transition patients off of denosumab, without resulting in an increased in BTMs. However, studies have shown overall good adherence to and patient satisfaction with denosumab compared to oral bisphosphonates, which may mitigate this concern [44].

Another major safety concern is infection risk, given RANKL inhibition of non-skeletal immune cells, causing a theoretical immune suppression. The extent of this risk remains unclear; although in FREEDOM extension the infection rates were similar to placebo [48], the initial FREEDOM data showed higher frequency of endocarditis (three in denosumab vs. zero in placebo group), and severe skin events (0.4% in denosumab vs. < 0.1% in placebo group, p < 0.05), suggesting a potential, but not definitive, increased risk of infections in immunocompromised patients [53]. Of note, rates of opportunistic infections were similar between denosumab and placebo groups.

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Box 1

Drug summary

Drug Name	Denosumab
Phase	Post-marketing
Approved Indications	Treatment of postmenopausal women with osteoporosis at high risk for fracture;
	Treatment to increase bone mass in men with osteoporosis at high risk of fracture; Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer; Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer
Mechanism of action	Suppression of bone resorption by binding to RANK ligand, preventing its binding to RANK and decreasing osteoclast formation, activity, and survival
Route of administrationChemical structure	Subcutaneous every 6 months(C6404 H9912 N1724 O2004 S50) consists of 2 heavy and 2 light chains; each light chain consists of 215 amino acids and each heavy chain consists of 448 amino acids with 4 intramolecular disulfides. Fully human monoclonal IgG2 antibody to RANK ligand
Pivotal trials	FREEDOM, ADAMO

Table 1

Selected Phase III and post-marketing clinical trials of denosumab

Study	Description	Primary Endpoint	Number of subjects	Efficacy results	Safety Results
FREEDOM [20]	Treatment of postmenopausal osteoporosis (denosumab vs. placebo)	New vertebral fractures at 36 months	7868	Denosumab reduced vertebral fracture risk	Similar AEs and SAEs, though cellulitis and eczema increased with denosumab
FREEDOM extension[31]	5 years of extension data beyond the 3-year FREEDOM trial	Efficacy and safety	2678 at 8 years of therapy	Continued reduction of vertebral and non-vertebral fracture risk	No new safety concerns during extension
ADAMO [38]	Treatment of osteoporosis in males (denosumab vs. placebo)	Change in LS BMD at 12 months	242	Greater BMD increase with denosumab	Similar AEs and SAEs
HALT [39]	Treatment of bone density loss in men undergoing androgen-deprivation therapy for non-metastatic, hormone-sensitive prostate cancer (denosumab vs. placebo)	Change in LS BMD at 24 months	1468	Greater BMD increase with denosumab. Decreased incidence of new vertebral fractures at 36 months	Similar AEs and SAEs
Denosumab in women receiving adjuvant aromataseIInhibitors for non-metastatic breast cancer [40]	Treatment of bone density loss in women with hormone receptor-positive non-metastatic breast cancer treated with adjuvant aromatase inhibitor (denosumab vs. placebo)	Change in LS BMD at 12 months	252	Greater BMD increase with denosumab	Similar AEs and SAEs
DATA [41]	Treatment of post-menopausal osteoporosis (teriparatide vs. denosumab vs. combination)	Change in LS BMD at 24 months	94	Greater BMD increase with combination therapy compared to single therapy	Similar AEs and SAEs
DAPS [44]	Patient satisfaction and adherence to treatment in post-menopausal women (denosumab vs. alendronate)	Proportion of subjects adherent to treatment at 1 year	221	Greater patient adherence to and satisfaction with denosumab	Similar AEs and SAEs

ADAMO: Study to compare the efficacy and safety of denosumab versus placebo in males with osteoporosis; AE: Adverse event; BMD: Bone mineral density; DAPS: Denosumab adherence preference satisfaction; DATA: Denosumab and teriparatide administration study; FREEDOM: Fracture reduction evaluation of denosumab in osteoporosis every 6 Months; LS: Lumbar spine; SAE: Serious adverse event;

Table 2

Comparison of major characteristics of bisphosphonates (alendronate and zoledronic acid) versus denosumab.

	Bisphosphonates		Denosumab
	Alendronate	Zoledronic Acid	
Efficacy	Vertebral and hip fracture reduction: ~ 50% (STAND and DECIDE trials comparing alendronate to denosumab showed greater BMD gains with denosumab at 12 months)	Vertebral fracture reduction: 70%. Hip fracture reduction: 41%. (Ongoing trial comparing efficacy of ZA vs denosumab)	Vertebral fracture reduction: 68%. Hip fracture reduction: 40%
Pivotal Trial	FIT [54]	HORIZON-PFT [55]	FREEDOM [20]
Safety	Risk for AFF and ONJ with prolonged exposure	Risk for AFF and ONJ with exposure to high doses and/or prolonged exposure	Risk for AFF and ONJ. Increased risk of serious skin infections
Administration	Oral, patient administered weekly	Intravenous administration once a year. Requires IV catheter placement	Subcutaneous injection every 6 months. Can be administered in office
Pharmacokinetics	Poor oral bioavailability. Non-uniform drug accumulation within bone matrix, with elimination half-life of ~ 10 years	Non-uniform drug accumulation within bone matrix, with prolonged suppression of bone turnover	No bone accumulation, effects reversible by 9 – 12 months post-dose
Pharmacodynamics	Slow suppression of bone turnover	More rapid suppression of bone turnover than oral (within days)	Rapid suppression of bone turnover (within 12 h)
Use in renal impairment	Contraindicated for GFR < 35	Contraindicated for GFR < 35	No restriction for use in renal impairment, though close monitoring of serum calcium in patients with GFR < 30 recommended
Relative cost	Low (generic available)	Moderate/High (generic available)	High

AFF: Atypical femur fractures; GFR: Glomerular filtration rate; ONJ: Osteonecrosis of the jaw.