

SIX-YEAR SAFETY AND EFFICACY DATA FROM DENOSUMAB PHASE 2 EXTENSION STUDY

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Denosumab (DMAb) is an investigational, fully human monoclonal antibody that inhibits RANKL, an essential mediator of osteoclast formation, function, and survival. DMAb has been shown to reduce the risk of vertebral, hip, and nonvertebral fractures after 3 years of treatment in the FREEDOM trial (Cummings *NEJM* 2009;361:756). In a phase 2 study, DMAb increased bone mineral density (BMD) and reduced bone turnover markers (BTM) after 4 years of treatment (Miller *Bone* 2008;43:222). Here we present the effects of 6 years of DMAb treatment on safety and efficacy with BMD and BTM. In the original phase 2 parent study, postmenopausal women with a DXA T-score between -1.8 and -4.0 (lumbar spine) or -1.8 and -3.5 (total hip or femoral neck) were randomized to receive placebo, alendronate (ALN), or 1 of 7 different doses of DMAb. After 2 years on study, subjects were reallocated to maintain, discontinue, or discontinue and reinitiate DMAb; discontinue ALN; or maintain placebo for 2 more years (Miller et al. *Bone* 2008). In a 4-year extension phase of this study, all subjects received open-label DMAb 60 mg subcutaneously every 6 months (Q6M). We report interim 2-year safety and efficacy analyses from the extension study, representing up to 6 years of exposure to DMAb.

For the 124 subjects who received 6 years of continuous DMAb treatment, BMD continued to increase over the entire treatment period: 13.3% at the lumbar spine, 6.1% at the total hip, and 1.9% at the 1/3 radius compared with their parent study baseline. For the 23 subjects in the previous placebo cohort, 2 years of DMAb treatment resulted in gains in BMD at all sites comparable to those observed during the first 2 years of DMAb 60 mg Q6M in the parent study.

Reductions in predose serum CTX and BSAP were sustained over the course of continuous DMAb treatment: the median reduction at year 6 was 55% for CTX and 42% for BSAP. Reductions in CTX and BSAP also were observed when the placebo group transitioned to DMAb treatment. Adverse events that occurred during the extension study were balanced and were similar to those observed during the parent study.

Continuous treatment with DMAb resulted in sustained reduction in BTM and further gains in BMD over a period of up to 6 years in postmenopausal women with low bone mass. The overall safety profile in this ongoing study extension did not change over time.

BMD RESPONSE TO DELAYED-RELEASE RISEDRONATE 35 MG ONCE-A-WEEK FORMULATION TAKEN WITH OR WITHOUT BREAKFAST

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Since their introduction, bisphosphonates (BPs) have become the first line treatment for postmenopausal osteoporosis. BPs have to be taken on an empty stomach at least 30 to 60 minutes before first food or drink. Here we present one year efficacy and safety results of a novel delayed release (DR) formulation of risedronate 35 mg once-a-week (OaW) that can be taken with or without breakfast.

This phase III study was designed to test the non-inferiority (based on the change in lumbar spine BMD from baseline at month 12) of the risedronate 35 mg OaW DR formulation taken before or after breakfast compared to the 5 mg daily immediate release (IR) dose taken per label. Participants were postmenopausal women at least 50 years of age, ≥ 5 years since last menses, with a lumbar spine T-score < -2.5 or a T-score < -2.0 with at least one prevalent vertebral fracture (T4 to L4). Patients were randomly assigned to risedronate 35 mg OaW DR following breakfast (FB) (n=307), or risedronate 5 mg IR daily (n=307) or risedronate 35 mg OaW DR at least 30 minutes before breakfast (BB) (n=308).

At one year, the mean percent change in lumbar spine BMD was 3.1% (95% CI, 2.71% to 3.53%) in the 5 mg IR daily group, 3.4% (95% CI, 2.94% to 3.77%) in the 35 mg DRFB group, and 3.4% (95% CI, 3.01% to 3.82%) in the 35 mg DRBB group. The mean difference (95% CI) between IR - DRBB was -0.296% (-0.873, 0.281) and between IR - DRFB was -0.233% (-0.816, 0.349). Because the CI of differences did not exceed the pre-defined non-inferiority boundary of $\pm 1.5\%$ (chosen based on data from previous studies), the risedronate 35 mg OaW DR formulation was shown to be non-inferior to the 5 mg IR daily whether taken before or after breakfast. The mean percent changes in BMD at the hip (total proximal femur, femoral neck, and femoral trochanter) were similar across groups, as were the changes in bone turnover markers. Both the 5 mg IR daily and the 35 mg OaW DR regimens were well tolerated. Adverse events were similar among the 3 groups.

Risedronate 35 mg OaW DR, whether taken before or after breakfast, provided similar efficacy and tolerability to daily treatment with risedronate 5 mg IR taken per the label.

EFFECT OF ONCE-YEARLY ZOLEDRONIC ACID 5 MG ON A SUB-SET OF SIX NON-VERTEBRAL FRACTURES

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Background: Bisphosphonates are widely used in the treatment of osteoporosis and are efficacious in reducing fracture risk. However, assessment of non-vertebral anti-fracture efficacy of bisphosphonates is not consistent in clinical trials due to differences in the definition of a non-vertebral fracture.

Methods: The Health Outcomes and Reduced Incidence with Zoledronic Acid One Yearly Pivotal Fracture Trial (HORIZON-PFT)¹ using intravenous zoledronic acid 5 mg (ZOL 5 mg) and Fracture Intervention Trial (FIT)² using oral alendronate, assessed anti-fracture efficacy of these drugs for non-vertebral fractures, which included all sites of fractures except the face, skull, fingers and toes and those due to excessive trauma (due to study design). HORIZON-PFT, a multicenter, double-blind, randomized, placebo-controlled study, involving 7736 women with postmenopausal osteoporosis (PMO), revealed significant reduction in the risk of non-vertebral fractures by 25% ($P<0.001$) with once-yearly i.v. ZOL 5 mg as compared to placebo at 3 years.¹ This *post-hoc* sub-analysis was done to determine the effect of ZOL 5 mg on a subset of 6 non-vertebral fracture sites (wrist, hip, pelvis, humerus, leg and clavicle) in HORIZON-PFT.

Results: ZOL 5 mg reduced the fracture risk in the subset of 6 non-vertebral fracture sites by 30% (95% CI: 8-47%; $p<0.01$) compared to placebo after 1 year and by 33% (95% CI: 21-44%; $p<0.0001$) after 3 years. The incidence of fractures at these 6 non-vertebral fracture sites in the ZOL 5 mg and placebo groups was 2.3% and 3.2%, respectively at 1 year and 5.9% and 8.8%, respectively at 3 years.³ ZOL 5 mg was well tolerated. Most adverse events were mild to moderate, occurring within 3 days post-infusion and resolved within 3 days of onset.¹

Conclusion: ZOL 5 mg significantly reduced the risk of fractures at the 6 non-vertebral fracture sites as early as 1 year in PMO and efficacy was maintained during 3 years of treatment.

References: 1. Black DM, *et al.* N Engl J Med. 2007;356:1809-22; 2. Black DM, *et al.* Lancet. 1996;348:1535-41; 3. Data on file, Novartis.

ZOLEDRONIC ACID SUBSTANTIALLY REDUCES THE RISK OF MORPHOMETRIC VERTEBRAL AND CLINICAL FRACTURES

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Background: HORIZON-Pivotal Fracture Trial (PFT) showed that a once-yearly infusion of zoledronic acid (ZOL 5 mg) during a 3-year period significantly reduced the risk of morphometric vertebral, hip, and all clinical fractures by 70%, 41%, and 33%, respectively.¹ As the fracture risk is not abolished and fractures beget more fractures, we sought to determine whether ZOL reduced the increased risk conferred by further fractures. In a pre-planned analysis, we examined the effect of once-yearly i.v. ZOL 5 mg in preventing a second morphometric vertebral fracture over 3 years and the recurrence of clinical fractures.

Methods: In the HORIZON-PFT, 7765 postmenopausal women with osteoporosis were randomized to an annual i.v. infusion of ZOL 5 mg ($n=3889$) or placebo ($n=3876$) for 3 years. Clinical fractures were reported by all patients to the investigator every 3 months. Lateral spine x-rays were done at randomization and yearly in patients not receiving concomitant osteoporosis therapy (stratum 1) and at randomization and end of study in patients receiving concomitant osteoporosis therapy (stratum 2). A multivariate proportional hazards regression model was used to evaluate the recurrence of clinical fractures in all patients stratifying for the usage of concomitant osteoporosis therapy (all intent-to-treat patients). Multiple morphometric vertebral fractures were evaluated using logistic regression adjusting for treatment and number of baseline prevalent fractures (stratum 1 and stratum 2 separately).

Results: Of the 308 (7.95%) postmenopausal women receiving ZOL who sustained a clinical fracture in HORIZON-PFT, 36 (11.7%) experienced 2 or more fractures. Of the 456 (11.81%) women receiving placebo who sustained a clinical fracture, 94 (20.6%) experienced 2 or more fractures. This corresponded to 38% reduction (95% CI: 28%, 46%) in the risk of multiple fractures ($p<0.0001$). ZOL reduces the risk of 2 or more morphometric vertebral fractures by 89% (95% CI: 77, 95) in stratum 1 and by 61% (95% CI: -23, 88) in stratum 2. The most common adverse events were transient post-infusion symptoms, which resolved within 3 days of onset.

Conclusion: In conclusion, once-yearly i.v. ZOL 5 mg substantially reduces the risk of multiple morphometric and clinical fractures suggesting that treatment mitigates the worsening fragility accompanying a fragility fracture.

References: 1. Black DM, *et al.* N Engl J Med. 2007;356:1809-22.

ODANACATIB IN THE TREATMENT OF POSTMENOPAUSAL WOMEN WITH LOW BONE MINERAL DENSITY: 3-YEAR CONTINUED THERAPY AND RESOLUTION OF EFFECT

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Background: The selective cathepsin K inhibitor odanacatib (ODN) progressively increased bone mineral density (BMD) and decreased bone resorption markers during 2 years of treatment in postmenopausal women with low BMD. A 1-year extension of this study assessed the efficacy and safety of ODN and the effects of discontinuing therapy.

Methods: During the base study, postmenopausal women with BMD T-scores between -2.0 and -3.5 at the lumbar spine, femoral neck, trochanter or total hip received placebo or ODN at 3, 10, 25 or 50 mg weekly. After 2 years, patients remaining blinded were re-randomized to ODN 50 mg weekly or placebo for an additional year. From the base study, 189 women continued into the extension, and 169 completed 3 years. Endpoints included BMD at the lumbar spine (primary), total hip and hip subregions, total body, and 1/3 radius; levels of biochemical bone turnover markers; and assessments of safety and tolerability.

Results: Continued treatment with 50 mg ODN for up to 3 years produced significant increases from baseline in spine (8%), total hip (6%), femoral neck (5%), and trochanter (7%) BMD and maintained BMD at the 1/3 radius. Serum NTx remained suppressed at Month 36 (-50%), but BSAP rose to slightly above baseline (18%) after an initial decrease. Treatment discontinuation resulted in bone loss at all sites, with higher rates in the initial 6 months and less loss between Months 30 and 36. At the end of Year 3, mean BMD among patients who took 50 mg ODN for 2 years and placebo in the third year was still above baseline at the femoral neck, was near baseline at the spine, and did not differ from placebo for total hip, trochanter, and 1/3 radius. Following ODN discontinuation, biochemical markers of bone remodeling increased rapidly above baseline values. This rebound in bone turnover occurred promptly after treatment discontinuation and largely resolved with time. For example, mean serum NTx reached 50% above baseline by Month 30, but was only approximately 28% above baseline by Month 36. No differences in the overall incidence of adverse events were observed between the pooled placebo and ODN treatment groups.

Conclusions: Three years of ODN treatment increased lumbar spine and hip BMD and was generally well-tolerated in postmenopausal women with low bone mass. Bone formation markers were relatively unaffected. BMD increases and resorption biomarker suppression with ODN were substantially reversed following discontinuation of treatment.

EFFECT OF SINGLE ANNUAL INFUSION OF ZOLEDRONIC ACID (5 MG) ON LUMBAR SPINE BONE MINERAL DENSITY VERSUS DAILY ORAL RISEDRONATE (5 MG) IN SUBGROUPS OF PATIENTS RECEIVING GLUCOCORTICOID THERAPY

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Background: Persistent use of glucocorticoid drugs is associated with bone loss and increased fracture risk. Prevention and treatment of glucocorticoid-induced osteoporosis is best established with bisphosphonates.¹ This 1-year, randomized, double-blind, study evaluated the effect of a single annual i.v. infusion of zoledronic acid (ZOL 5 mg) compared to daily oral risedronate (RIS 5 mg) on lumbar spine bone mineral density (LS BMD) in different subgroups of patients receiving glucocorticoid therapy.

Methods: Patients were divided into two subpopulations according to glucocorticoid treatment duration at randomization; treatment subpopulation (>3 months [ZOL, n=272; RIS, n=273] and prevention subpopulation (≤3 months [ZOL, n=144; RIS, n=144]). Later, they were further divided into subgroups by gender, age (aged <35, 35-50, 51-64, 65-74, ≥75 years), mean prednisone dose during the trial (<7.5, ≥7.5 to <12, >12 mg/d), and the history of other medications.

Results: ZOL 5 mg significantly increased LS BMD compared to daily oral RIS 5 mg from baseline to 12 months for both men ($p<0.05$) and women ($p<0.01$) in the treatment and prevention subpopulations. This significant increase in LS BMD by ZOL compared to RIS was also observed in different subgroups of age, mean prednisone dose ≥7.5 to <12 mg/d, with/without the prior history of other medications in both the subpopulations (Table). Adverse events were common across both the study groups but transient post-dose symptoms were higher with ZOL during the first 3 days of treatment, which resolved within 3 days of onset.

Conclusion: A single annual i.v. infusion of ZOL 5 mg significantly increases LS BMD to a greater extent compared to the daily oral RIS 5 mg in different subgroups of glucocorticoid-treated patients.

References: 1. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. *Arthritis Rheum.* 2001;44:1496-503.

Table. Significant increase in LS BMD by ZOL compared to RIS in different subgroups

Subpopulation	Subgroups	p value
Treatment	Age: 35-40 yrs	0.0041
	51-64 yrs	0.0075
	Prior history of other medication Anti-tumour necrosis factor	0.0278
Prevention	Prior history of other medication Proton pump inhibitor	0.0148
Treatment and prevention	Age: 65-74 yrs	<0.05
	Mean prednisone dose: ≥7.5 to <12 mg/d	<0.001
	No prior history of other medications	
	Proton pump inhibitor	<0.01
	Anti-tumour necrosis factor	<0.01
	Selective serotonin reuptake inhibitor	<0.0001

EFFICACY OF ORAL IBANDRONATE VERSUS 3 MG INTRAVENOUS IBANDRONATE

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BACKGROUND: Ibandronic acid is a potent, nitrogen-containing bisphosphonate used in the treatment of osteoporosis; it is available like 150 mg film-coated tablet for once monthly oral administration and 3 mg intravenously every 3 months. There is strong patient preference for once-monthly regimen and a favourable impact on therapeutic adherence. Intravenous ibandronate formulation is indicated for all patients who are unable to take oral medicine.

METHODS: This study evaluates the efficiency of ibandronate after 1 year of oral / i.v. administration for osteoporosis in postmenopausal women. We present the results of a retrospective study which included 2 groups of women that were registered in The National Programme of Osteoporosis. The first group consisted of 50 women with oral administration of ibandronate; the other group of 25 women received ibandronate intravenously for an year. The average age was 64.51 y.o. in the first group and 65.7 y.o. in the second one, in postmenopausal period for 13/18 years, with a T score of 3.43 ± 0.66 SD / 3.5 ± 0.7 SD at the beginning of the study.

RESULTS: After one year of therapy the biological parametres as calcemia and alkaline phosphatase improved and the bone turn-over markers-cross-laps and osteocalcin-decreased (reduction of 50% for cross laps and 33% for osteocalcine in the oral regimen and of 38 % for cross-laps and 9,5% for osteocalcine in the i.v. regimen). Both oral and i.v. ibandronate significantly increased bone density at the spine (4.3% and 5.8% vs. baseline with oral and intravenous ibandronate, respectively) Significant increases were also observed for total hip bone density (1.9% vs. baseline for the oral formulation and 2.6% vs. baseline for the i.v. administration). Percentage of patients with no change or increase from baseline in bone mineral density was high in both groups (Lumbar spine 94% for the oral formulation vs. 96% for i.v. and Total hip 92% vs 84%)

There were no recurrent fractures and no serious adverse events reported in either one of the groups.

CONCLUSION: Both formulations of ibandronate were shown to improve the quality of life, to reduce the risk for recurrent fractures and increase of bone mineral density after one year of therapy. IV ibandronate was shown superior to the oral formulation regarding lumbar BMD, total hip BMD and the percentage of BMD responders.