Osteoporosis – Present and Future
Sponsor: MSD

SY1. OSTEOPOROSIS IN ASIA: STRATEGIES IN ADDRESSING UNDER-TREATMENT AND VITAMIN D INADEQUACY

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Recent advances in development of effective anti-osteoporosis agents has rendered this previously neglected disease treatable with significant impact in reducing fracture and improving quality of life.

Unfortunately, treatment gaps continue to plague the satisfactory management of osteoporosis. This appears to be a global phenomenon, not only affecting developing but also developed countries. In recent surveys of patient management after osteoporotic fractures in Asian countries, this unfortunate problem is probably even more acute. K. Dai (Shanghai, China) reports that if a sample of 2855 records reviewed, only 14% of patients hospitalised for osteoporotic hip fractures were treated for osteoporosis on discharge.

Physician and population awareness continue to be major obstacles. Among Healthcare Professionals, Ip et al report that of a total of 204 doctors who responded to a questionnaire survey, only 76% actually treated patients for the disease, citing inaccessibility and high cost of diagnostic modalities (DXA) and therapeutic agents as reasons for the non-initiation of therapies. In a population survey conducted in Singapore (Saw et al), only 58% of respondents had heard of osteoporosis and of these, only 79% were concerned about developing osteoporosis and only 15% were aware that osteoporosis was more prevalent than cancer.

Adequate calcium and vitamin D are integral to achievement of optimal bone health. In addition, vitamin D is important for normal neuromuscular function. Awareness for need of adequate calcium is universal although translating this to actual adequate intake/supplementation may still be less than optimal. The critical role that vitamin D plays is even less well appreciated, not only by the lay public but also by clinicians. Countries in Asia - both temperate and subtropical have a high prevalence of vitamin D inadequacy and deficiency. This problem is underestimated and often overlooked, in particular in countries in the tropical region like Malaysia, Thailand and Singapore - where the ‘mistaken’ belief is that there is adequate sunshine throughout the year (without the variations of seasons) to fulfill our needs. In a recent review, the incidence of vitamin D inadequacy in postmenopausal women with osteoporosis ranged from 50% HK, 47% Japan, 22–64% S Korea, 11% Malaysia and 12% Thailand (when 25OH Vit D <20 ng/ml was used as the cutoff point). The prevalence escalates to 47–92% if <30 ng/ml is applied.

Strategies for effective management of osteoporosis in the Asian region have to take into account the above gaps and remain a big challenge.

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SY2. TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS: WHO AND HOW LONG TO TREAT

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There are now many pharmacologic interventions that have been shown in double blind placebo controlled trials to decrease the risk of vertebral fracture and in some instances non-vertebral fracture risk. At present there are few comparator studies so that treatments are given largely on the basis of effect and side effect profiles tailored to individual patient needs. The question of how long to treat is not resolved, but important considerations are offset time (the time for effects of treatment effects to resolve when treatment is stopped) and adherence. Against this background, greater progress has been made in identifying who best benefits from treatment and conversely those in whom treatment may be less worthwhile.

At present, treatment is largely directed on the basis of bone mineral density (BMD). In the UK, for example, treatment is recommended when the T-score for BMD is found to be less than –2.5 SD. The same T-score has, however, quite a different significance at different ages. The 10-year probability of hip fracture for women in the UK with a T-score of –3 SD is 3.2% at the age of 50 years, but 19.8% at the age of 80 years. Thus, fracture risk prediction is optimised by integrating information on risk factors that contribute to fracture risk independently of BMD. A major programme of the WHO Collaborating Centre at Sheffield has been to identify and validate readily used risk factors from prospective population-based cohorts that have been incorporated into fracture risk prediction tools (FRAX™). Clinical risk factors that contribute to fracture risk independently of BMD include age, previous fragility fractures, a family history of fracture, rheumatoid arthritis, smoking, exercise, alcohol and the use of oral glucocorticoids. Their combined use with (or without) BMD enhances the sensitivity of fracture prediction without sacrificing specificity. Because the risk of fracture varies markedly around the world, particularly the risk of...
hip fracture, assessment models need to be calibrated to the epidemiology of the country in which they are to be used. Models are available for several countries including France, Italy, Japan, Spain, Sweden, the USA, and the UK.

The ability to assess fracture risk from clinical risk factors permits intervention in men and women that is based not solely on BMD but on the ten year probability of fracture. Therefore, diagnostic thresholds for osteoporosis (based on BMD) differ from intervention thresholds. The setting of intervention thresholds is ultimately dependent on national considerations and guidance is required to determine the fracture probability at which to intervene, both for treatment (an intervention threshold) and for BMD testing (assessment thresholds). These are currently being developed for Europe, Japan, the UK and USA. In the UK, guidance has being developed by the National Osteoporosis Guideline Group (NOGG). The intervention threshold at each age is set at a risk equivalent to that associated with a prior fracture and, therefore, rises with age. For the probability of a major fracture, this varies from 7.7% to 30%.

**SY3. ODANACATIB CLINICAL UPDATE: A NEW MECHANISM TO TARGET BONE REMODELLING**

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Odanacatib is a novel therapy for osteoporosis that selectively inhibits cathepsin K in osteoclasts. It appears to reduce osteoclastic bone resorption without decreasing osteoclast number. The viable osteoclast is thought to play a role in communication with osteoblasts to maintain osteoblastic bone formation despite the reduction in osteoclastic bone removal.

In a phase Ib randomized double-blind study, 399 postmenopausal women (age 64.2±7.8 years) with low bone mineral density (BMD) were treated initially for 1 year with 1 of 4 doses of this new agent or placebo along with calcium and vitamin D replacement. The enrolled women had BMD T-scores ≤−2.0 at the lumbar spine, total hip, femoral neck or hip trochanter and ≥−3.5 at all sites. Of these, 320 women continued into a second year and 280 completed 2 years of treatment. Participants and investigators remained blinded to treatment throughout. Endpoints included BMD and biochemical indices of bone turnover, along with standard safety outcomes. Skeletal turnover was assessed via transilial biopsies in a subset (N=27) at the end of 2 years.

There were progressive dose related increases from baseline in BMD with the three highest doses of odanacatib. Lumbar spine and total hip BMD increased 5.5% and 3.2% with 50 mg once weekly and were virtually unchanged in the placebo group (−0.2% and −0.9%). Markers of bone turnover [urinary N-telopeptides (NTx/Cr) and serum bone-specific alkaline phosphatase (BSAP)] decreased 52% and 13%, respectively, with the 50 mg dose. By contrast, these markers were virtually unchanged with placebo. Translational biopsy data are consistent with modest suppression of bone formation: bone formation rate for the three highest doses was decreased only 17–35% and activation frequency was decreased only 16–51%, without any dose related trend in either parameter. Osteoclast surface appeared unaffected. There were no safety signals of note.

In this study over two years, odanacatib increased lumbar spine and total hip BMD with only minor reduction of bone formation in postmenopausal women with low BMD. It also appeared to have a reassuring safety profile. Fracture endpoint studies are underway to clarify the effect of this novel agent on fragility fracture risk.

**New Frontiers in Assessment of Fracture Risk**

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**SY4. VERTEBRAL AND NON-VERTEBRAL FRACTURES - EPIDEMIOLOGY**

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Osteoporotic fractures are a significant source of morbidity and cost to health care systems around the world. In the USA alone, the annual direct costs of osteoporosis exceed $18 billion in 2002 dollars; hip fractures account for 63% of that cost. The estimated lifetime risk of an osteoporotic fracture for a 50-year-old woman in Europe is as high as 50% and for a hip fracture between 15% and 20%. Due to shifts in population and life expectancy, the burden of hip fractures is dramatically increasing in the developing world. Although the majority of hip fractures worldwide currently occur in Europe and North America, by 2050 the vast majority, as much as 80%, will occur in Asia and Latin America.

During the past 20 years, we have made great strides in predicting fractures using diagnostic tools and risk factor assessment. BMD has been demonstrated to be a robust predictor of each type of fracture, and age, gender and race are now recognized as key risk factors. Other important risk factors include personal and family history of hip fracture, weight, height and smoking history. In general, risk factors seem to operate similarly around the world, supporting the validity of using a single risk index (FRAX™) universally. However, there are some interesting exceptions. For example, although BMD among Asians is generally lower than in Caucasians, hip fracture risk is also lower in Asians. This suggests a possible difference in the relationship of BMD to fracture in Asians compared to Caucasians.

Costs and consequences of individual types of fractures have been studied worldwide for various types of fractures. Hip fractures are the most costly individual types of fractures and are responsible for significant morbidity, but hip fractures account for only a minority of total fractures and less than half of the morbidity associated with non-vertebral fractures. A study in Minnesota showed that among women, hip fractures accounted for less than 20% of all fractures. In the Fracture Intervention Trial, between 60% and 75% of days of disability attributable to non-vertebral fractures were due to non-vertebral fractures other than hip fractures. The relative importance of non-vertebral fractures other than hip fractures to total morbidity of non-vertebral fractures varies by age. The Minnesota study showed that non-hip fractures represented approximately 55% of the incremental costs and the morbidity for all fractures in women older than 80 years but as much as 80% to 90% of the costs among women in their 50s.

In conclusion, using BMD and risk factors, we can predict the occurrence of hip, spine, and non-vertebral fractures well. The
FRAX index allows us to predict hip and non-vertebral fractures for individual patients. Although the consequences of hip and spine fractures are dramatic, we should also consider the cumulative impact of non-vertebral fractures other than hip fractures among osteoporotic patients in their 50s, 60s, and 70s.

SY5. FRACTURE RISK, FRAX™ AND RESPONSE TO TREATMENT

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FRAX™ is a computer based algorithm (http://www.shef.ac.uk/FRAX) that provides models for the assessment of fracture probability in men and women. The approach uses easily obtained clinical risk factors, with the optional input of femoral neck bone mineral density (BMD), to estimate 10-year fracture probability. FRAX™ has been constructed using the primary data of population based cohorts from around the world, including centres from North America, Europe, Asia, and Australia. The gradients of fracture risk have been validated in independent cohorts with a similar geographic distribution. The large sample permits the examination of the general relationship of each risk factor by age, sex, duration of follow up, and; for continuous variables (BMD and BMI); the relationship of risk with the variable itself, in a manner hitherto not possible to improve the accuracy of prediction. Unlike many other algorithms, FRAX™ also derives hazard functions of death as well as fracture using the same clinical risk factors and Poisson regression. The FRAX™ output is the 10-year probability of major osteoporotic fracture (hip, clinical spine, shoulder, or wrist fracture) and the 10-year probability of hip fracture alone.

The application of FRAX™ to clinical practice will demand a consideration of the fracture probability at which to intervene, both for treatment (an intervention threshold) and for BMD testing (assessment thresholds). These are currently being developed for Europe, Japan, UK, and USA. Also, it is important to establish that patients identified at high risk by the algorithm are responsive to anti-resorptive treatment. Such evidence is now forthcoming. For example, in a large placebo-controlled study of women aged 75 years and older, recruited regardless of the presence or absence of osteoporosis, treatment with clodronate 800 mg daily demonstrated more evident efficacy in those deemed at highest risk. Thus in women lying at the 75th percentile of fracture probability in the absence of BMD (10-year probability 24%) treatment reduced fracture risk by 27% whereas in those with a fracture probability of 30% (90th percentile), the fracture risk reduction was 38%. Similarly, in an analysis of the pivotal anti-fracture study of bazedoxifene, which combined both tested doses compared to placebo, hazard ratios for the effect of bazedoxifene on all clinical fractures decreased with increasing fracture probability. In patients with 10-year fracture probabilities at or greater than 17% (the 80th percentile), bazedoxifene was associated with a significant decrease in the risk of all clinical fractures. The efficacy of bazedoxifene on morphometric vertebral fractures also increased at higher fracture probability, and at any probability was more marked than that on all clinical fractures, e.g., at the 90th percentile of FRAX™ probability, bazedoxifene reduced all clinical fractures by 31% and reduced morphometric vertebral fractures by 51% reduction.

The FRAX™ tool for estimating an individual’s 10-year probability of fracture is able to identify patients at high risk of fracture who will respond to therapy with clodronate or bazedoxifene. Such analyses are now a requirement of the CPMP and it will be of value to confirm these observations with other efficacious treatments.

RANK Ligand Inhibition: A Future Strategy for the Management of Postmenopausal Osteoporosis?
Sponsor: AMGEN

SY6. RANK LIGAND INHIBITION AS A NEW CONCEPT IN TARGETING THE OSTEOCLAST

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The architecture of cortical and trabecular bone is maintained by constant remodelling, reflecting a balance between osteoclast-mediated bone resorption and osteoblast-mediated bone formation. An imbalance in bone remodelling, resulting from enhanced bone resorption, can induce increased bone loss, such as in osteoporosis. This makes the osteoclast a natural target for therapeutic intervention to prevent bone loss. The currently available major class of drugs for osteoporosis, bisphosphonates (BPs), act by binding strongly to bone mineral and by being internalised by bone-resorbing osteoclasts, thereby impairing osteoclast function.

The formation, function and survival of osteoclasts are dependent on receptor activator of NF-κB ligand (RANK Ligand) binding to RANK on the surface of osteoclasts and their precursors. This interaction is inhibited by osteoprotegerin (OPG), a naturally occurring decoy receptor that competes with RANK for binding to RANK ligand. Thus, inhibiting RANK ligand may be an alternative approach to inhibit osteoclast-mediated bone loss.

Transgenic overexpression of OPG in rats resulted in increased bone mass and strength, consistent with a marked decrease in bone resorption [1]. Histomorphometry from this study revealed significant reductions in osteoclasts and bone turnover parameters in OPG-Tg rats versus WT controls.

In an arthritis rat model, both OPG-Fc and a BP, zoledronate, were able to prevent the development of osteopenia as measured at the lumbar vertebrae [2]. However, bone preservation with OPG was associated with reductions in RANK ligand and the RANKL:OPG ratio and decreases in the number of osteoclasts. In contrast, zoledronate treatment was associated with an increase in RANK ligand and RANKL:OPG ratio, without any apparent decreases in the number of osteoclasts. These observations suggest a different mechanism of action of these molecules.

Denosumab is the first fully human monoclonal antibody in late stage clinical development that specifically binds and inhibits RANK ligand. In ovariectomised cynomolagus monkeys, long-term (15 month) treatment with denosumab increased bone mass and bone density at both cortical and trabecular sites. These increases were highly correlated with improvements in extrinsic (whole bone) strength. In the same animal model, transition from a BP (alendronate) to denosumab resulted in further reductions in bone turnover, further
inhibits bone resorption by specifically targeting RANK ligand, a key mediator of osteoclast formation, function and survival.

The efficacy and safety of denosumab were compared with alendronate in a phase 3 trial involving 1,189 postmenopausal women (mean age, 64 years) with low BMD, with 594 women receiving denosumab and 595 receiving alendronate [1]. Treatment naive postmenopausal women with T-score $\leq -2.0$ at the lumbar spine or total hip were randomised 1:1 to receive double-blind, double-dummy, subcutaneous denosumab 60 mg q6m or oral alendronate 70 mg q1w over 12 months.

Denosumab significantly increased total hip BMD (primary endpoint) compared with alendronate (treatment difference 1%, p$< 0.0001$) [1]. Significantly greater gains in BMD with denosumab were also seen at the trochanter, 1/3 radius, lumbar spine and femoral neck (p$\leq 0.0003$ at all sites). Significantly greater reductions in the bone turnover markers, serum c telopeptide (sCTx) and procollagen type I N propeptide (P1NP), occurred with denosumab compared with alendronate at months 1 and 6 (p$< 0.0001$ for sCTX and p$< 0.0001$ for P1NP, the latter also was significant at month 12). Safety profiles were similar between treatment groups and no patients developed neutralising antibodies to denosumab.

In a 12-month, double-blind, randomised phase 3 trial of postmenopausal women with low BMD (lumbar spine or total hip T-score $\geq -4.0$ and $\leq -2.0$), the effects of transitioning from weekly alendronate to denosumab on BMD were compared with continued alendronate therapy [2]. Greater gains in BMD were observed at all sites measured (including total hip, lumbar spine, femoral neck, distal radius and hip trochanter) in subjects who received twice yearly denosumab after transitioning from alendronate therapy, as compared with those who continued receiving weekly alendronate. The incidence and type of adverse events observed in this study were well balanced between treatment groups.

Denosumab, a RANK ligand inhibitor, demonstrated greater gains in BMD compared with alendronate both in treatment naive patients as well as in patients previously treated with alendronate.

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SY7. THE THERAPEUTIC POTENTIAL OF RANKL INHIBITION IN PATIENTS WITH LOW BONE MASS

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Osteoporosis is characterised by an excess of bone resorption, leading to decreases in bone mineral density (BMD), reduced bone strength and increased fracture risk. Bisphosphonates are commonly used to treat osteoporosis. Denosumab, an investigational fully human monoclonal antibody, suppresses osteoclast-mediated bone resorption by specifically targeting RANK ligand, a key mediator of osteoclast formation, function and survival.

The efficacy and safety of denosumab were compared with alendronate in a phase 3 trial involving 1,189 postmenopausal women (mean age, 64 years) with low BMD, with 594 women receiving denosumab and 595 receiving alendronate [1]. Treatment naive postmenopausal women with T-score $\leq -2.0$ at the lumbar spine or total hip were randomised 1:1 to receive double-blind, double-dummy, subcutaneous denosumab 60 mg q6m or oral alendronate 70 mg q1w over 12 months.

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SY8. THE EFFECT OF RANK LIGAND INHIBITION ON FRACTURE OCCURRENCE IN PATIENTS WITH POSTMENOPAUSAL OSTEOPOROSIS

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Osteoporosis is defined by the WHO as a bone mineral density (BMD) value of $\leq -2.5$ standard deviations below the mean value of a young healthy population (T-score $\leq -2.5$). Although BMD presents a convenient marker for assessing the efficacy of osteoporosis treatment, the key clinical goal is to reduce risk of fracture.

Hip and vertebral fractures are among the fractures most associated with osteoporosis. However, osteoporotic fractures at other sites (e.g., humerus, ankle, distal forearm and foot) also have a considerable impact, and such fractures account for a substantial proportion of the burden of osteoporotic fractures in women [1]. Therefore, reduction of fracture risk at all skeletal sites represents an important treatment goal.

Denosumab is an investigational, fully human monoclonal antibody that targets RANK ligand an essential mediator of osteoclast formation, function and survival throughout the skeleton. In clinical trials of postmenopausal women with bone loss, treatment with denosumab decreased bone resorption and increased BMD at vertebral, hip and distal forearm sites. Results from the FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months) study will provide important data on vertebral and non-vertebral fracture risk reduction in postmenopausal women treated with denosumab.

FREEDOM is a randomised, double-blind, placebo-controlled multicenter phase 3 study involving postmenopausal osteoporotic women. Women aged 60–90 years with a lumbar spine or total hip T-score $< -2.5$ and $\geq -4.0$ were randomly assigned to receive 60 mg s.c. denosumab, or matching placebo, every 6 months for 3 years. All participants received 1000 mg/day elemental calcium and 400–800 IU/day vitamin D. The primary outcome measure
was the risk of new vertebral fractures and secondary outcomes included the risk of non-vertebral fractures and hip fractures.

A total of 7,868 women (mean age 72.3 years) were recruited from 214 clinical centres in 32 countries. The primary and secondary outcome measures and safety results will be presented.

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New Tactics for Skeletal Health Preservation
Sponsor: ELI LILLY

SY9. EFFECTS OF ANTI-RESORPTIVES ON BONE QUALITY IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS

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Suppression of bone resorption is a well established, powerful treatment regime of osteoporosis, as evidenced by reduction of fragility fracture incidence with bisphosphonates or SERM treatments in large clinical trials during the 1990s. One representative trial, the FIT alendronate study, showed 7–8% increase of BMD with 50% reduction of fracture incidence, while the MORE Raloxifene study showed only 3% increase of BMD with 49% reduction of vertebral fracture incidence. The results of these clinical trials imply that BMD is not a sole factor to determine bone strength. In 2001, an NIH consensus statement recognized bone quality as an important determinant of bone strength besides BMD. Bone quality includes bone architecture, microdamage, mineralization as well as collagen crosslinks, which are all controlled by bone remodeling. Antiresorptives suppress excessive bone turnover in osteoporosis, while bone resorption also plays an important part in bone remodeling, which removes old bone tissue before new bone formation. It is important to know the function of bone remodeling in adult bone to optimize antiresorptive treatment. By suppressing bone resorption, bone mass and degree of mineralization of bone increase and trabecular and cortical architectures are reinforced, while microdamage and degenerative collagen crosslinks (pentosidine) accumulate in bone. Bone becomes stiffer and tougher by suppressing bone resorption initially; however, if over suppression of bone resorption occurs, bone becomes brittle and reduces toughness. Monitoring bone turnover and bone quality, if possible, will become important to optimize osteoporotic drug treatment for individual patients.

SY10. SERMS FOR PREVENTION OF FRACTURE AND INVASIVE BREAST CANCER: WHO SHOULD BE TREATED?

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Selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene reduce the risk of breast cancer by binding to the estrogen receptor and blocking the effect of estrogen in the breast. Both reduce the risk of estrogen receptor positive (ER+) breast cancer by at least 50%, and ER + cancer accounts for most breast cancer that occurs in postmenopausal women. The Study of Tamoxifen and Raloxifene (STAR) trial compared raloxifene and tamoxifen in women at high risk of breast cancer and showed that they had the same efficacy for preventing invasive breast cancer. Raloxifene did not appear to lower risk of non-invasive breast cancer.

Recent studies have also shown that the decreased risk of breast cancer - and death from breast cancer - continues for at least 10 years after stopping a 5-year course of tamoxifen. Limiting the costs and potential adverse effects to 5 years with at least 10 more years of reduced breast cancer risk makes chemoprevention a more cost-effective approach to prevention of breast cancer. This extended effect on risk of breast cancer probably applies to all antiestrogens, but there are no specific data for raloxifene.

Raloxifene and tamoxifen differ in other ways. Raloxifene has also been shown to reduce the risk of vertebral fracture and is approved in the USA and many other countries for prevention and treatment of osteoporosis. The STAR trial found that raloxifene was less likely than tamoxifen to cause venous thromboembolic events and cataracts. Raloxifene was significantly less likely to cause endometrial hyperplasia or lead to hysterectomy. Other trials have found that tamoxifen, but not raloxifene, increases the risk of endometrial cancer. Tamoxifen, but not raloxifene, increases the risk of stroke. Raloxifene should be avoided in elderly women who have a high risk of stroke because it may increase the risk of stroke and death in those women. Overall, raloxifene appears to be the best choice for prevention of breast cancer in most postmenopausal women.

Studies suggest that realistic decreases in weight, increases in exercise, and decreases in alcohol intake may reduce breast cancer risk by 10–20%. These are important parts of prevention of breast cancer. However, women at high risk of breast cancer should consider chemoprevention.

The ideal candidate for raloxifene would be a woman at high risk of breast cancer and vertebral fracture. The effect of raloxifene on breast cancer risk may be considered when choosing treatment to prevent fracture. In USA women, studies have found that a simple combination of age >60 and a family history of breast cancer indicates at least a 2.5% 5-year risk of breast cancer. Postmenopausal women with high breast density also have an increased risk of breast cancer.

SY11. SAFETY PROFILE OF SERMS: FOCUS ON THE UTERUS

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Raloxifene interacts with estrogen receptors in many tissues. Its most important benefits are the prevention of vertebral fractures and reduction in risk of breast cancer. The MORE study showed that raloxifene improved bone density and reduced the risk of vertebral fracture by 30–55%, with a greater reduction within the first year of treatment. The RUTH trial which focused on cardiovascular endpoints confirmed that raloxifene reduces the
risk of clinical vertebral fracture by about 35%. Clinical vertebral fractures cause, on average, about 3 months of acute disability, often followed by persistent pain and impaired function. Raloxifene had no significant effect on the risk of nonvertebral fracture in the primary analysis of the data from either trial. As with all estrogens and tamoxifen, raloxifene increases the risk of deep venous thrombosis. Treatment with raloxifene may also cause hot flushes, arthralgia/myalgia, oedema, and leg cramps, each in less than 5% when compared to placebo.

In 2006, two large scale raloxifene clinical trials were published, the Raloxifene Use for The Heart (RUTH) and the Study of Tamoxifen and Raloxifene (STAR) P-2 trial.

RUTH was a double-blind, placebo-controlled international trial of 10,101 postmenopausal women (mean age 67.5 years) at increased risk for coronary events. The two primary endpoints were invasive breast cancer and coronary events. In RUTH (median follow up, 5.6 years), the incidence of invasive breast cancer was 44% lower in the raloxifene 60 mg/d group versus placebo (hazard ratio 0.56, 95% CI 0.38–0.83) and the incidence of coronary events was similar in both treatment groups (HR 0.95, 95% CI 0.84–1.07). In conclusion, the RUTH trial showed that raloxifene did not significantly affect the risk of cardiovascular disease. In these women with or at high risk of cardiovascular disease, there was a possible increased risk of fatal stroke. Interestingly, there was also a statistically significant reduction in non-cardiovascular mortality.

The STAR trial was sponsored by the National Surgical Adjuvant Breast and Bowel Project (NSABP), conducted in North America, and designed to compare the relative effects of raloxifene 60 mg/d and tamoxifen 20 mg/d on the risk of developing invasive breast cancer and other disease outcomes in women at increased risk of breast cancer (N=19,747, mean age 58.5 years). In STAR (mean follow up, 3.9 years), the incidence of invasive breast cancer was similar in the raloxifene and tamoxifen group, there were fewer VTE events and cataracts (p<0.01 in both cases), as well as numerically fewer uterine cancers (p=0.07). In the tamoxifen group, there were numerically fewer non-invasive breast cancers (p=0.052). There was no difference between treatment groups in the incidence of overall mortality, coronary events, stroke or osteoporotic fractures.

It is important to balance the potential benefits and risks of raloxifene. An analysis of the “global” benefits and risks on major diseases suggested a favourable overall balance for postmenopausal women with osteoporosis. Assessing and balancing the risks of fracture, breast cancer, and cardiovascular disease should be a routine part of health care for postmenopausal women.

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SY12. EFFECTS OF TERIPARATIDE TREATMENT IN PATIENTS WITH GLUCOCORTICOID-INDUCED OSTEOPOROSIS

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Glucocorticoid therapy is the most common secondary cause of osteoporosis. The resulting bone loss and fractures are associated with reduced bone formation at both the tissue and cellular level, caused by decreased osteoblastogenesis and increased apoptosis of osteoblasts and osteocytes. Whilst preventive and therapeutic strategies have previously focused mainly on anti-resorptive therapy, drugs that stimulate bone formation have an important potential role. The aim of this randomised, double-blind, double-dummy active comparator controlled trial was to compare the effect of teriparatide, an anabolic agent, and the anti-resorptive drug alendronate, on lumbar spine bone mineral density (BMD) in patients with glucocorticoid-induced osteoporosis.

428 patients (83 men) receiving ≥5 mg prednisolone or equivalent daily for at least 3 months were randomised to receive a subcutaneous injection of teriparatide 20 μg/day or oral alendronate 10 mg/day. All patients received calcium and vitamin D supplements. Inclusion criteria included a BMD T-score≤−2 at the lumbar spine, total hip or femoral neck or ≤−1 plus at least one fragility fracture. The primary analysis was conducted after 18 months of treatment.

At baseline, demographic characteristics were similar in the two treatment groups with a mean age of 56 and 57 years in the teriparatide and alendronate groups, respectively (range 22–89). The most common underlying diagnosis in both groups was rheumatoid arthritis (46% and 52%, respectively). 68.7% of patients completed the study.

After 18 months, the increase in lumbar spine BMD was significantly greater in patients treated with teriparatide than in those treated with alendronate (7.2±0.7 vs. 3.4±0.7%; p<0.001),...
this between-group difference being observed as early as 6 months (p<0.001). Significantly greater increases in BMD were also seen in the total hip in teriparatide treated patients compared with the alendronate group. The incidence of morphometric vertebral fractures (a secondary endpoint) was 6.6% vs. 6.1% in the teriparatide and alendronate groups, respectively (p=0.004); no significant difference in non-vertebral fractures was seen between the two groups. Significantly more patients in the teriparatide group had elevated serum calcium values on at least one occasion.

In conclusion, 18 months treatment with teriparatide in patients with glucocorticoid-induced osteoporosis is associated with significantly greater increases in the lumbar spine and proximal femur compared with alendronate. Significantly fewer morphometric vertebral fractures occurred in teriparatide treated patients. These results are consistent with a role for teriparatide in the management of glucocorticoid-induced osteoporosis.

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SY13. BONE MODELLING AND REMODELLING: THE HEART BEAT OF A LIVING TISSUE

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Bone’s material composition and structural design determine its ability to tolerate loads without fracturing. Bone responds to loads by modifying, adapting its material composition and structure to accommodate these loads and does so remarkably during growth as can be seen by the effects of exercise in athletes.

Adaptation is achieved by bone modelling and remodelling which modifies structure by depositing bone where it is needed and removing bone from were it is not needed. After closure of the epiphyses, age-related changes compromise the ability of this cellular machinery to modify bone structure. The earliest change is a decline in bone formation in the basic multicellular unit (BMU), so less bone is deposited after damaged bone is removed. In addition, the volume of bone resorbed in each BMU probably actually decreases but less so than the decrease in formation, so the net effect is a negative BMU balance. Every time a remodelling event occurs bone is lost from the skeleton. At menopause, remodelling rate increases and remains elevated, the life span of osteoclasts increases so the volume of bone resorbed increases, at least temporarily. Bone formation also decreases on the periosteal surface as well as within each BMU shortly after closure of the epiphyses. In addition, collagen becomes crosslinked by advanced glycation endproducts such as pentosidine.

These changes alter the material composition, macro-, micro- and nano-structure of bone. The negative BMU balance and high remodelling produce cortical thinning and porosity, trabecular thinning and loss of connectivity. Reduced volume of bone resorbed in each remodelling cycle may produce smaller osteons, so the number of osteons per unit volume of bone falls, offering less obstruction to crack propagation in the relatively larger interstitial bone between osteons. As interstitial bone is deep to remodelling, it is older, more densely and homogeneously mineralised and more crosslinked by pentosidine. These features increase propensity for crack initiation and propagation. Reduced osteocytic density in interstitial bone reduces the ability to detect damage and so to remove it. If bone formation is reduced in the BMU due to reduced osteoblast numbers, then reduced synthesis of osteocytes may occur. Reduced periosteal bone formation contributes to fragility because endocortical resorption is not compensated for, so there is both failure to offset cortical thinning and failure to shift the cortical bone outwards from the neutral axis, a change that increases resistance to bending.

Ideally, therapeutic agents should increase bone formation in the BMU and reduce bone resorption in the BMU. If bone balance in the BMU is made positive, treatment should maintain or increase the rate of remodelling so that each remodelling event deposits bone. If bone balance in the BMU remains negative, the drug should reduce the rate of remodelling. The drug should modify the osteocyte lifespan, increasing the production or reduce apoptotic death of osteocytes. It should reduce nonenzymatic crosslinking of collagen and increase periosteal apposition.

SY14. A PHYSIOLOGICAL APPROACH FOR BETTER BONE QUALITY

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The depletion in estrogens occurring at menopause leads to an imbalance in the fine tuned process of bone remodeling, resulting in bone loss and microarchitectural deterioration of bone tissue, subsequently leading to an increase in bone fragility.

The goal of any antiosteoporotic treatment is a reduction in the resulting increased risk of fracture. Anti-resorptive and anabolic agents reduce the risk of fracture by either suppressing or stimulating the activation frequency of bone remodelling units. By a coupling effect, however, agents downregulating bone resorption also decrease bone formation, and agents upregulating bone formation also increase bone resorption.

The question arises whether an agent could decrease the risk of fracture through acting with an optimal mechanism of action, by working on both sides of the equation. Strontium ranelate appears to provide the answer with its unique dual mode of action, increasing bone formation at the same time as decreasing bone resorption. The evidence for the dual mode of action of strontium ranelate is provided by in vitro and in vivo studies demonstrating both a stimulating effect on osteoblasts and an inhibiting effect on osteoclasts.

This dual effect has been further confirmed by changes in bone markers and in bone biopsy parameters observed during phase 3 studies addressing the anti-fracture efficacy of strontium ranelate.

This innovative treatment positively influences bone remodeling by at least two identifiable mechanisms: an increase in osteoblast replication, partly mediated by an agonist effect on the calcium-sensing receptor, and a downregulation of osteoclast differentiation due to an increase in osteoblast expression of OPG, coupled with a decrease in RANK-L expression.
The dual effect of strontium ranelate on bone remodelling results in an improvement of both bone microarchitecture and intrinsic bone properties, without significantly affecting the activation frequency of basic multicellular units. Strontium ranelate acts through physiological effects on bone remodelling, accounting for the proven efficacy of this agent to prevent the risk of vertebral, non-vertebral and hip fractures.

**SY15. STRONTIUM RANELATE: CLINICAL BENEFITS CONFIRMED IN ASIAN POPULATION**

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Osteoporosis is a major public health problem in the growing ageing population in Asia. Strontium Ranelate (SR) is an antosteoporotic treatment simultaneously reducing bone resorption while promoting bone formation. SR has proven efficacy in reducing the risk of fracture and increasing bone mineral density (BMD) in Caucasian postmenopausal women. Limited data is available on the response of Asian women to antosteoporotic treatment. To evaluate the efficacy of SR in Asian postmenopausal women, a meta-analysis was performed on 3 multi-centered studies conducted in Mainland China-Hong-Kong-Malaysia, Korea and Taiwan. These studies shared a similar protocol and allowed a preplanned meta-analysis of the results. The aim was to evaluate the efficacy of SR (2 g/day) in comparison with placebo on BMD changes over 1 year, and to show the similarity of results obtained in the Asians compared to Caucasians from the European phase 3 SOTI (Spinal Osteoporosis Therapeutic Intervention) study.

All together 562 Asian postmenopausal osteoporotic women were studied (302 patients from Mainland China, Hong Kong and Malaysia, 135 Korean and 125 Taiwanese), with 282 patients in SR group and 280 patients in placebo group. The mean age was 65.6 years, with the time since menopause of 17.2 years and mean lumbar spine BMD T-score of −2.8. The baseline characteristics were similar in both treatment groups and also similar to those observed in the Caucasian study.

SR-treated patients had a significant increase in BMD over 12 months of 5.2±5.1% at the lumbar spine, 3.0±4.7% at the femoral neck, and 3.2±3.7% at the total hip, while no significant change was found in the placebo group (between-group difference p<0.0001). The degree of BMD improvement is strongly consistent with those observed in the Caucasian population, where SR has proven an early and sustained efficacy in reducing new vertebral fracture (49% over one year and 41% over 3 years) associated with a significant increase in lumbar spine BMD of 5.9% over one year.

Overall, this meta-analysis of studies performed in Asian osteoporotic postmenopausal women confirmed the efficacy of SR in increasing BMD and the results are strongly consistent with those obtained in the SOTI study referenced for bridging. Based on the strong relationship between a sustained increase in BMD and fracture risk reduction with SR, the same level of antifracture efficacy of SR is expected in Asians as in Caucasians.

**SY16. TREATING BONE AS A LIVING TISSUE: A STEP FORWARD IN FRACTURE PREVENTION**

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Fractures resulting from osteoporosis are a major cause of morbidity and mortality in postmenopausal women. Particularly, 20% to 24% mortality has been reported in the first year after a hip fracture. The incidence of osteoporotic fractures is expected to increase dramatically in the coming years, particularly in Asia: the results of the Asian Osteoporosis study confirmed that the hip fracture incidence rates in Hong Kong and Singapore were approaching those observed in American Caucasians.

While only 30% of all hip fractures in the world occurred in Asia in 1990, it is forecasted that more than 50% of them will occur in this continent by the year 2050.1

To reduce this burden is thus a priority. Patients with osteoporosis require an effective and safe treatment, easy to use on the long term. Strontium Ranelate has proven its efficacy to reduce vertebral, non-vertebral and hip fractures, over 5 years vs. placebo, and recent data confirm that this efficacy is maintained over 8 years.

This efficacy was shown to be independent of all risk factors increasing fracture risk, such as age, bone mineral density, prevalent fractures, and the bone turnover at baseline.

This wide range of efficacy is confirmed in patients considered as difficult to treat:

- Strontium ranelate is the first treatment having proved its efficacy to reduce the risk of vertebral and non-vertebral fractures in elderly osteoporotic women aged 80 years and over.
- The clinical efficacy of strontium ranelate was recently confirmed in younger patients, aged 50–65 years, in whom a strong decrease in BMD is observed right after menopause.
- In patients having previously being treated by bisphosphonates, beneficial effects on bone quality after a one-year treatment with strontium ranelate were clearly demonstrated in an analysis of human paired biopsies.

Moreover, strontium ranelate was shown to significantly improve the well being of the patients, by preventing height loss, by increasing the number of patients free of back pain, and by improving their quality of life.

In addition to its efficacy to prevent fractures in osteoporotic women, strontium ranelate reduces the progression of thoracic kyphosis, a risk factor for vertebral fractures influencing quality of life. This action is demonstrated regardless the presence or not of vertebral fractures.

Furthermore, strontium ranelate significantly delays spinal osteoarthritis progression in osteoporotic patients with prevalent spinal OA.

All these evidence support the use of strontium ranelate as a first choice treatment for all women with osteoporosis.

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Emerging Clinical Evidence in the Differences Among Bisphosphonates

Sponsor: THE ALLIANCE FOR BETTER BONE HEALTH

SY17. INTERPRETING CLINICAL TRIAL DATA: HOW IMPORTANT ARE THE DIFFERENCES BETWEEN BISPHOSPHONATES?

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The primary goal of osteoporosis therapy is to prevent fractures because they are associated with considerable morbidity and mortality. After the first osteoporotic fracture, the risk for subsequent fractures increases dramatically. Thus, both in those who have not yet sustained an osteoporotic fracture and those who have suffered from one, measures to prevent fractures are critically important.

The bisphosphonates represent a major therapeutic class for the prevention and treatment of osteoporosis. Although changes in bone density and bone turnover markers help to account for the reduction in fracture incidence with bisphosphate therapy, they are only partly explanatory. Other indices are likely to account for their actions and there may be differences among the bisphosphonates in terms of their scope of efficacy and speed of onset.

Four bisphosphonates (alendronate, ibandronate, risedronate and zoledronate), currently approved in the USA and most of Europe for the treatment of osteoporosis, have been shown in 3-year pivotal clinical trials to reduce the risk of vertebral fractures. Post hoc analyses suggest differences among them with regard to speed of reduction in the risk of clinical vertebral fractures. Alendronate, risedronate and zoledronate, in prospective trials, have all been shown to reduce the risk of nonvertebral fractures and hip fractures. Differences among bisphosphonates may be discernable with regard to onset of protection from nonvertebral fractures.

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SY18. CONSEQUENCES OF DIFFERENCES IN STRUCTURE-FUNCTION RELATIONSHIPS AMONG BISPHOSPHONATES

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All bisphosphonates (BPs) used as inhibitors of bone resorption contain two phosphonate groups attached to a single carbon atom, and are, therefore, stable analogues of naturally occurring pyrophosphate-containing compounds. This helps to explain their intracellular, as well as their extracellular, modes of action. The side chain substituents determine their potency both in terms of mineral binding and cellular actions. The pharmacological potency of individual BPs in vivo is determined by the combination of their avidity for bone mineral and their potency on their molecular targets within cells, especially osteoclasts.

All of the more potent, nitrogen-containing BPs appear to act principally by inhibiting farnesyl diphosphate synthase (FPPS), a key enzyme in the mevalonate pathway of cholesterol biosynthesis. Inhibition of FPPS prevents the biosynthesis of isoprenoid compounds that are essential for the posttranslational modification of small GTPases, involved in osteoclast activity. The structure of human FPPS and its interactions with inhibitory BPs have now been extensively characterised. Together with new insights into the differential mineral binding properties of BPs, we are closer to explaining the persistence of action of different BPs, as well as their potency.

Thus, there are obvious chemical, biochemical and pharmacological differences among the various BPs that could account for clinically relevant differences, including effects on hip and nonvertebral sites, speed of onset of effect and speed of offset. Each of the BPs has its own unique profile.

There are now data from both clinical trials and observational studies that suggest differences exist among BPs. In particular, these data support the concept that risedronate has an earlier effect on fracture risk than alendronate.

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SY19. BEYOND RANDOMISED CONTROLLED TRIALS: REAL-LIFE EFFECTIVENESS IN OSTEOPOROSIS MANAGEMENT

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Randomised placebo-controlled clinical trials are the gold standard to determine the efficacy of a drug and are often specifically designed to satisfy strict regulatory criteria. By nature, they require a fixed study design with narrowly defined study populations, dosing schedules and treatment periods. In the real world, patients have multiple comorbidities, use other concomitant medications and present many conditions which would exclude approximately 80% of these subjects from clinical trials. Nevertheless, these patients may be prescribed osteoporosis drugs, raising the question of treatment effectiveness in clinical practice.

Considering the growing number of therapeutic options in osteoporosis, it would also be desirable to have between-treatment comparisons in order to evaluate which drugs are most effective. Unfortunately, prospective head-to-head comparison trials with fracture as the primary outcome have not been conducted in osteoporosis so far. Nevertheless, some studies using data obtained from healthcare plans in the USA have started to evaluate the effectiveness of anti-resorptive drugs in relation to the onset of fracture reduction in clinical practice.

The large REAL (RisedronatE and ALendronate) study was conducted to investigate the incidence of hip and nonvertebral fractures in the year following initiation of once-weekly risedronate or alendronate. REAL was a retrospective cohort study observing the incidence of nonvertebral and hip fractures in risedronate and alendronate-treated female patients within healthcare utilisation records in the USA. Differences in fracture incidence were observed at both 6 and 12 months after therapy initiation. Following one year of therapy, the incidence of nonvertebral and hip fractures in the risedronate cohort was 18% and 43% lower than in the alendronate cohort, respectively.

In order to further test the robustness of the results from REAL, additional analyses were performed, which included a subgroup analysis of patients with a previous fracture history (n=2845), and therefore most likely to have osteoporosis. Within this subgroup, patients receiving risedronate had a 66% lower incidence of hip fractures compared to patients receiving alendronate at one year. In order to evaluate the actual anti-fracture efficacy of risedronate and alendronate in this observational study, we also performed a new comparison with a pseudo-control group of patients (n=3002) who were prescribed bisphosphonates but were not treated beyond one month. Results indicate that risedronate significantly reduced hip fractures compared to the controls, whereas alendronate did not.

Well designed observational studies, such as REAL, provide new insights into osteoporosis drug effectiveness in the real life and thereby may be helpful to guide therapeutic choices beyond primary efficacy results.

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New Clinical Evidence in the Treatment of Vertebral Compression Fractures: Balloon Kyphoplasty vs. Non-surgical Management

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SY20. IS CONSERVATIVE MANAGEMENT CONSERVATIVE? THE IMPACT OF VERTEBRAL BODY COMPRESSION FRACTURES TREATED NON-OPERATIVELY ON HEALTH AND QUALITY OF LIFE

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There are approximately 750,000 vertebral body compression fractures (VCFs) secondary to osteopenia in the United States each year, and the rate of fracture in Europe and Asia is similar. While about 30-40% of VCFs come to medical attention, many symptomatic fractures are not diagnosed due to the insidious nature of osteoporotic vertebral body collapse, often not apparent at onset of symptoms.

Although palliative care has been considered appropriate in most cases, the consequences of bed rest in the elderly are not benign, and prospective studies document decrements in quality of life following clinically evident VCF, including a lack of improvement in physical function domains at one- and two-year follow-up. The loss of quality of life is similar to, or exceeds, that of patients with hip fracture at all follow-up times.

However, whether the fracture is painful or not, the spine develops a kyphotic deformity, even with optimal osteoporosis treatment. Vertebral fracture occurrence is a potent independent risk factor for future fracture. This increase in fracture risk is partly explained by the biomechanics of the spine, because kyphosis increases vertebral body loads.

There is substantial evidence that the kyphotic deformity, independent of acute fracture pain, has a profound impact on patient health, quality of life and survival. Patient quality of life after VCF remains impaired compared to matched norms as long as five years after the last clinically-evident fracture. Quality of life also...
decreases with each additional fracture. The loss of quality of life created by 1–2 VCFs managed non-operatively is similar to that seen in patients with COPD and hypertension, while the loss of quality of life created by 3 or more VCFs managed non-operatively is similar to that seen in patients with cancer or congestive heart failure.

Patients with osteoporotic kyphotic deformity also have decreased pulmonary function related to thoracic restriction created by the kyphotic deformity14–17, diminished physical performance18,19, digestive and nutritional disturbances20, and impaired gait which reduces mobility and increases the risk of falls.20,21 VCF are associated with an increased risk of death22–24 and is greater than the excess risk of death from hip fractures.25,26

The current literature on the outcomes of non-operative care of symptomatic VCFs strongly suggests that a safe and effective intervention to address acute fracture pain, restore physical function and diminish kyphotic deformity, is appropriate.

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SY21. BALLOON KYPHOPLASTY - A MINIMALLY INVASIVE PROCEDURE FOR VERTEBRAL COMPRESSION FRACTURES

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In the 1980s, radiologists in France treated painful vertebral bodies containing defects caused by haemangiomas by injecting liquid polymethylmethacrylate (PMMA) bone cement into the vertebral body through needles under fluoroscopic guidance. Later on they applied this technique, which they called vertebroplasty, for symptomatic fragility fractures of the spine due to metastases and osteoporosis. Vertebroplasty was based on the immediate and long-term clinical success of filling defects created by benign tumors with PMMA bone cement in areas of the body which experience significant compressive loads, notably the hip and knee.

KYPHON® Balloon Kyphoplasty is a minimally invasive orthopaedic spine procedure for patients with one or more vertebral compression fractures caused by osteoporosis, cancer or benign lesions, as well as trauma.

The procedure is designed to stabilise the fracture and correct the vertebral body deformity. Through bilateral 1 cm incisions a 6 Francisco and extra-pedicular into the vertebral body. Via these workshafts, two orthopaedic balloons are guided into the fractured vertebral body. The balloons are gently inflated in an attempt to raise the collapsed vertebra, creating a void inside the vertebral body.

The main advantage of the KYPHON® Inflatable Bone Tamps (balloons) is that an en masse reduction of a compression fracture can be achieved through a small incision in a majority of cases. The balloon is a unique reduction instrument because it has the ability to apply even pressure by adapting to the irregular surface of the bone. It is designed to compress cancellous (trabecular) bone and move cortical bone in order to achieve fracture reduction.

Once the fracture has been reduced (i.e., restored towards its pre-fracture height and configuration), the balloons are deflated and removed.

The vertebral body is then stabilised at its repaired height by filling the void with viscous bone cement in a controlled manner under low manual pressure. The procedure typically takes about an hour per fracture treated. After the procedure, the patient should return to the referring physician for medical management and follow-up of the underlying disease that caused the fracture.

SY22. FRACTURE REDUCTION EVALUATION (FREE) - A RANDOMIZED TRIAL OF BALLOON KYPHOPLASTY AND NONSURGICAL CARE FOR PATIENTS WITH ACUTE VERTEBRAL COMPRESSION FRACTURES: 1 YEAR RESULTS

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Balloon kyphoplasty is a percutaneous procedure for reducing pain, and improving function and quality of life, in patients with painful vertebral fractures. Balloon kyphoplasty has not been tested in a randomized trial.

Clinical data comparing surgical interventions with non-operative care are rare and, in fact, there are few randomized clinical studies supporting the surgical care of any osteoporotic fracture, including hip and wrist.

In 1999, shortly after balloon kyphoplasty for the treatment of symptomatic VCFs became available, a USA-based multicenter randomized controlled clinical study, comparing patients undergoing the procedure with patients managed nonoperatively, was initiated. 39 centers participated, but, after two years, only 40 patients were enrolled. Of the 20 patients in the
non-operative arm, 14 received kyphoplasty within a month, a protocol violation. The study was stopped due to enrollment difficulties.

In 2003, a group of European physicians was organized to conduct a similar study, addressing some of the recruitment difficulties in the USA-based study. Ultimately, 19 centers participated, including 5 each in Germany and France, 2 each in Sweden, the UK, Italy and Belgium, and 1 in the USA.

Enrollment began in February 2003 and completed in December 2005. Among the main entry criteria, patients ages 40–85 were study candidates if they had 1–3 VCFs associated with back pain (VAS score ≥4) showing edema on MRI and a 15% loss of midline or anterior vertebral body height in at least one of the fractures. Patients with traumatic VCFs, neurologic symptoms, unable to walk prior to fracture, or unable to participate in the study and its two year follow-up, were excluded.

Patients with up to 3 nontraumatic acute vertebral fractures were randomly assigned to kyphoplasty (N=149) or nonsurgical care (N=151). The primary study endpoint is the Physical Component Summary score of SF-36. Secondary endpoints include other SF-36 domains, the Roland-Morris back disability questionnaire, the Numeric Rating Scale (VAS) back pain score, a patient satisfaction questionnaire, health care utilization and EQ-5D. All endpoints are assessed at 1, 3, 12 and 24 month follow-up. The back pain VAS is also assessed at 7 days. Deformity correction and maintenance of lost vertebral height restored are assessed at 3, 12 and 24 months. Safety is continuously monitored throughout the study, with all adverse events, serious adverse events, subsequent fractures and cement leaks documented.

One year results will be presented.

Reference:
http://clinicaltrials.gov/ct2/show/NCT00211211

SY23. BALLOON KYPHOPLASTY FOR PATIENTS WITH PAINFUL VERTEBRAL COMPRESSION FRACTURES: JAPANESE STUDY

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Introduction: Vertebral augmentation is now a very common procedure for painful osteoporotic and osteolytic vertebral compression fractures worldwide. However, even with a rapidly growing and aging population in Japan, there is no official surgical code for vertebral augmentation approved by the Japan Ministry of Health Labor and Welfare. One of the main reasons is that the Japanese society is still wondering whether the use of polymethylmethacrylate (PMMA) in vertebral augmentation is safe for elderly patients. In September 2005, a Japanese multicenter 2-year study of balloon kyphoplasty to treat painful osteoporotic vertebral compression fractures (VCFs) was initiated. Here the interim clinical results of this study will be presented.

Methods: Patients with one acute (<8 weeks old) vertebral compression fracture (VCF) due to primary osteoporosis were included in the study. The acute fracture was confirmed by Magnetic Resonance Imaging (MRI). The patients with burst fractures and with more than 3 VCFs (≥2 chronic VCFs) were excluded. Bone mineral density (BMD) <80% (Young Adult Mean) was confirmed by dual-energy X-ray absorptiometry (DXA). Balloon kyphoplasty was performed on the patients whose painful VCF did not respond to a minimum of 8 weeks of conservative treatment. Pain score using visual analogue scale (VAS), Short-form 36 (SF-36), subsequent fracture rate, and the extent of vertebral body height restoration were measured at each time point (7 days, 1, 3, 6, 9, 12, 15, 18, 21, and 24 months) with follow-up out to 2 years after surgery.

Results: A total of 81 patients met the inclusion criteria and underwent balloon kyphoplasty. There were no intra-operative complications directly associated with PMMA, and only one postoperative complication which required anterior spinal reconstruction due to cement migration. Balloon kyphoplasty subjects had significantly less back pain on a 0 to 10-point numeric rating scale at seven days (2.4 points; p<0.0001) and has remained low.

Conclusion: The interim results of this Japanese study show balloon kyphoplasty is a safe and effective treatment for patients with painful VCFs. Complications directly associated with PMMA are very low. Vertebral body heights of the fractured vertebra were well restored by balloon kyphoplasty. Optimum timing of this surgical intervention still needs to be determined.

Improving Bone Strength and Reducing Fractures: A Review of Current Evidence

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SY24. THE SIGNIFICANCE OF SURROGATE MARKERS IN FRACTURE OUTCOMES

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In women with postmenopausal osteoporosis, loss of bone mass due to an imbalance in bone resorption and formation results in increased fracture risk.

- Increased levels of bone turnover markers along with loss of BMD are established surrogate markers for fracture risk in postmenopausal osteoporosis.
- Daily oral bisphosphonates have demonstrated antifracture efficacy versus placebo. The less frequently dosed, oral bisphosphate regimens have been compared in clinical trials to daily regimens and have been proven to be at least as effective as their equivalent daily regimens for lumbar spine BMD gains and reductions in bone markers. BMD results were non-inferior for:
  - weekly alendronate: 6.8% vs. 7.4%, respectively, (2 years)
  - weekly risedronate: 4.7% vs. 5.2%, respectively, (2 years)
  - monthly risedronate: 3.5% vs. 3.4%, respectively, (1 year).
• In the MOBILE study, superior gains in lumbar spine BMD were seen at all sites measured in spine and hip with monthly oral ibandronate 150 mg versus daily at 2 years.\(^4\)
  
  – In the long term extension study (LTE) of the Mobile Trial, patients receiving monthly ibandronate 150 mg for 3 years showed additional increases in BMD, where lumbar spine BMD increased by 7.6%; \(p<0.0001\) vs. baseline.\(^5\)

• Data from the MOBILE study also showed that a large number of patients treated with monthly oral ibandronate responded to treatment\(^4\)
  
  – a high proportion of patients experienced BMD gains at or above baseline at both the lumbar spine and total hip (≥90%) and at prespecified cutoff points for lumbar spine (≥6%; 53%) and total hip (≥3%; 65%) consistent with those reported to be indicative of antifracture efficacy.\(^3,6\)

• Reductions in bone markers are also reported with bisphosphonates
  
  – levels of the marker of bone resorption serum C-telopeptide of the alpha chain of type 1 collagen (sCTX) were substantially reduced within 3 months of treatment with monthly oral ibandronate 150 mg and remained reduced throughout the 2 years of MOBILE and year 1 of the LTE.\(^4,5\)
  
  – reductions in urinary crosslinked N-telopeptides of type I collagen (uNTX) and bone-specific alkaline phosphatase (BSAP) were reported for alendronate with similar levels of suppression shown for daily and weekly regimens.\(^1\)
  
  – daily and weekly (2 years) risedronate also showed reductions in uNTX, sCTX and BSAP\(^2\)

• While risedronate weekly and monthly regimens demonstrated at one year generally similar reductions in uNTX and BSAP, the monthly regimen demonstrated significantly lower suppression of CTX at all measured time points.\(^3\)

Conclusion

Compared with their respective daily regimens, weekly alendronate and weekly and monthly risedronate show similar efficacy in terms of BMD gains. Alendronate has demonstrated similar reductions in bone markers with its daily and weekly regimen, while risedronate results suggest potentially lower suppression with the monthly regimen. Ibandronate regimens used in clinical practice (150 mg monthly oral and 3 mg quarterly i.v.) compared to the daily regimen demonstrated superior BMD gains and greater suppression of bone turnover that was superior at most time points. These results demonstrate the positive changes in the critical components of bone strength delivered by ibandronate to provide robust fracture protection.

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SY26. IBANDRONATE: A FOCUS ON ANTI-FRACTURE EFFICACY

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Postmenopausal osteoporosis is a chronic condition associated with increased morbidity and mortality, occurring as a result of vertebral and non-vertebral (including hip) fragility fractures.1 The primary aim of osteoporosis treatment is fracture prevention.

- Ibandronate (2.5 mg daily) has demonstrated a superior vertebral fracture relative risk reduction (RRR) compared with placebo (62%; p<0.0001).2
- Bone mineral density and bone turnover marker data indicated monthly oral 150 mg and quarterly i.v. injection 3 mg ibandronate may provide greater fracture protection than daily oral ibandronate (2.5 mg).
- To test this hypothesis, a meta-analysis was conducted using individual patient data3–two studies with a similar study design were included: MOBILE (monthly oral ibandronate)3 and DIVA (intermittent i.v. ibandronate injection)4—the meta-analysis was performed, maintaining original study randomisation to increase validity, by experts in meta-analyses and osteoporosis—annual cumulative exposure (ACE), a calculation of total annual absorbed dose that provides a common scale for effective biological activity across oral and i.v. regimens, was used to allow grouping of doses—relative risk for fracture was expressed as hazard ratios using Cox regression analysis, including adjustment for baseline differences.

- Compared with daily oral ibandronate 2.5 mg (ACE 5.5 mg), higher ibandronate doses, including the licensed 150 mg monthly oral, 3 mg quarterly i.v. injection, and unlicensed 2 mg every 2 months i.v. injection (ACE ≥10.8 mg), significantly reduced the risk of non-vertebral fractures at 2 years by 38% (HR=0.620; 95% CI 0.395, 0.973; p=0.0375)5—time to non-vertebral fracture was also extended for higher versus low doses of ibandronate (p=0.036) and a dose-response effect was observed, with a trend towards higher doses resulting in greater antifracture efficacy.

- The VIBE (eValuation of IBandronate Efficacy) study is a large observational study of two longitudinal medical and pharmaceutical USA claims databases (i3 Research and i3 Innovus IMPACT)6—primary objective: to compare fracture rates in patients treated with monthly oral ibandronate or weekly bisphosphonates (alendronate/risedronate)—study population: women with osteoporosis or osteopenia, aged ≥45, who were bisphosphonate-naïve for 6 months prior to study commencement and remained in the database for ≥3 months following enrollment.

- The primary analysis population included patients adherent to treatment (≥90 days) who were followed for 12 months or until first fracture, non-persistence (refill gap of 45 days for monthly ibandronate, 30 days for weekly bisphosphonates) or they switched therapy.

- Results showed no significant difference in rates for non-vertebral, hip or any fracture between ibandronate and weekly bisphosphonates. However, there was a statistically significant lower rate of vertebral fractures in the ibandronate group than in the weekly bisphosphonate group.

Conclusion

The findings from the VIBE observational, database study add to the data on nonvertebral efficacy reported from the randomised clinical trials and meta-analysis.5,6 In the VIBE study, ibandronate reduced the risk of non-vertebral and hip fractures in patients with postmenopausal osteoporosis to a similar extent as other oral bisphosphonates. The vertebral fracture rate was significantly lower with monthly ibandronate versus weekly bisphosphonates; however, the clinical significance of this finding warrants further validation.

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