Observational Study Protocol

A prospective, observational, non-comparative, open-label study to investigate the effectiveness of the treatment with weekly Alendronate in postmenopausal women with Osteoporosis.

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1. SYNOPSIS

Study Title: A prospective, observational, non-comparative, open-label study to investigate the effectiveness of the treatment with weekly Alendronate in postmenopausal women with Osteoporosis.

Objectives:

The primary objective of this study is to evaluate Bone Mineral Density (BMD) changes at lumbar spine of Greek osteoporotic women from baseline to 12th month from the initiation of Alendronate 70mg once weekly.

The secondary objectives of this study are to estimate new vertebral and non-vertebral fragility fractures, hip fractures, treatment compliance, occurrence of back pain and days lost from work due to fracture related back pain from baseline to 12th month from the initiation of Alendronate 70mg once weekly. Also, to evaluate the safety of Alendronate assessed by the type, frequency, and severity of ADRs for 18 months after the initiation of study.

Design and Outcomes:

This is a Greek observational prospective study of 12 months to evaluate the effect of Alendronate 70mg once weekly on BMD change (%) at lumbar spine in postmenopausal women. The decision to treat the patient with Alendronate must be made independent of and prior to their enrollment in the study. Patients eligible to participate will receive their prescription monthly.

Primary Outcome:

- BMD change (%) at lumbar spine at 6,12 months of treatment measured by DXA

Secondary Outcomes:

- the proportion of patients with severe osteoporosis experiencing one or more new vertebral and non-vertebral fragility fractures assessed by spine radiographs regardless of symptoms
- Compliance to therapy, self-reported by patients
- Days lost from work due to fracture-related back pain, self reported by patients

Secondary Safety Outcomes:

- the proportion of patients with ADR to Alendronate
- the proportion of patients with serious ADR to Alendronate

Treatment Procedures and Duration:

Patients will return to the clinic every month to receive their Alendronate 70mg prescription. Patients will be observed for a period of up to 12 months after their entry in the study and will be followed up for 6 months after their last visit.

Sample Size and Population:

Inclusion criteria: Postmenopausal women who are diagnosed with osteoporosis.

Exclusion criteria: Previous treatment with drugs that modify bone metabolism or serious bone/esophageal/renal disease.

Approximately 512 patients need to be enrolled in the study to achieve the desired precision. Patient pool will be the orthopaedic clinic of Larisa Public Hospital.

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3. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
BMD	Bone Mineral Density
BMI	Body Mass Index
DXA	dual energy X-ray absorptiometry
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EOF	National Organization for Medicines
IRB	Institutional Review Board
PMO	Post Menopausal Osteoporosis
SADR	Serious Adverse Drug Reaction
SID	Study Identification Number
WHO	World Health Organization

4. STUDY OBJECTIVES

Primary objective:

Evaluate Bone Mineral Density (BMD) changes at lumbar spine of Greek osteoporotic women from baseline to 12th month from the initiation of Alendronate 70mg once weekly.

Secondary objectives:

Evaluate new vertebral and non-vertebral fragility fractures, hip fractures, treatment compliance, occurrence of back pain and days lost from work due to fracture related back pain from baseline to 12th month from the initiation of Alendronate 70mg once weekly.

Also evaluate the safety of Alendronate assessed by the type, frequency, and severity of ADRs for 18 months after the initiation of study.

5. BACKGROUND

Disease

Osteoporosis is described by the World Health Organization as a 'progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[1] Osteoporosis is a major public health threat; in a recent review, the prevalence of osteoporosis was reported as an estimated 200 million people worldwide while about 40 to 50% of women are at risk of having an osteoporotic fracture in their lifetimes.[2,3] Nonetheless, most women with osteoporosis remain asymptomatic, which makes epidemiological research especially difficult.[4] Osteoporosis related fractures are associated with significant morbidity and mortality. Their non-fatal consequences include pain, physical impairment and loss of functional ability, which can have significant adverse effects on patient quality of life. There are also substantial costs to society in terms of diminished activity, hospitalization and lengthy stays in nursing homes as well as days lost from work.[5]

A diagnosis of osteoporosis can be made on the base of either fractures occurring without significant trauma or low bone mineral density measured by dual energy X-ray absorptiometry (DXA).[6]

According to the WHO diagnostic classification, osteoporosis in Caucasian women is defined as a bone mineral density (BMD) at the hip or lumbar spine that lies 2.5 standard deviations or more below the average for the young healthy female population (T-score <-2.5 S.D.).[6] Osteoporosis can be treated effectively mainly by antiresorptive agents, such as bisphosphonates, by anabolic agents, such as parathyroid hormone analogues, by denosumab which is a fully human monoclonal antibody that inhibits RANKL, by strontium, and by raloxifen a selective estrogen receptor modulator.[7,8] Other non-pharmacological strategies suggested

to reduce the burden of osteoporosis are smoking cessation and exercise.[9] Bisphosphonates represent a major advance in osteoporosis treatment and remain at the forefront of medications used for years with great efficacy and safety for the care of patients.[10]

Drug background

Alendronate is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localization of Alendronate to sites of active resorption. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with Alendronate is of normal quality.[11]

Alendronate is approved for the prevention (5 mg daily and 35 mg weekly tablets) and treatment (10 mg daily tablet, 70 mg weekly tablet) of postmenopausal osteoporosis. Alendronate is also approved for treatment to increase bone mass in men with osteoporosis and for the treatment of osteoporosis in men and women taking glucocorticoids.[1] In the initial efficacy studies of Alendronate, the mean bone mineral density (BMD) increases with Alendronate 10 mg/day relative to placebo at three years with 8.8%, 5.9% and 7.8% at the spine, femoral neck and trochanter, respectively. Total body BMD also increased significantly. Also, Alendronate reduces the incidence of spine and hip fractures by about 50 percent over three years in patients with a prior vertebral fracture or in patients who have osteoporosis at the hip site. It reduces the incidence of vertebral fractures by 48 percent over three years in patients without a prior vertebral fracture. [12]

Rationale

Even though regulatory approval has been granted for Alendronate many years ago, no large observational study has been conducted in Greek population to collect information on patient characteristics including demographics, comorbid conditions and use of concomitant medications and thus ensure that the drug is being used in patients that it was intended to. Moreover, findings of such a study will help describe women receiving Alendronate for osteoporosis in Greece highlighting at the same time the factors determining therapeutic choice and the patient's fracture risk; comorbid conditions influencing bone health (including systemic, metabolic, rheumatic, thyroid, parathyroid, renal and lung); clinical factors related to osteoporosis (prior fracture, age, ambulatory status, bone turnover markers, BMD T-score, body mass index, Ca (calcium) and vitamin D intake; lifestyle factors (smoking, alcohol and drug use/abuse); and socioeconomic status (employed, retired). In addition, Alendronate efficacy will be confirmed in Greek population.

6. STUDY DESIGN

This is a Greek observational prospective study to evaluate the effect of a biphosphonate drug, Alendronate, on BMD in postmenopausal women for a total period of 12 months. This observational study will not alter the routine clinical management of patients and will comply with all applicable local regulations of Greece. The decision to treat the patient with Alendronate must be made independent of and prior to their enrollment in the study. It is expected that patients eligible to participate will receive their first prescription during their initial clinic appointment and thereafter once monthly along with local standard clinical care according to clinical judgment and international guidelines. Approximately 512 patients will be enrolled in the study. The first 512 patients that will attend the orthopaedic clinic of Larisa Public Hospital and will be deemed appropriate candidates for biphosphonates treatment will be eligible to participate in the study. Detailed data obtained as part of routine clinical practice will be collected at the initial visit directly from patients or through their past medical record. These will comprise of demographic patient data, medical condition, risk factors for osteoporosis, and comorbidities. It is anticipated that patients will return to the clinic every month to receive their Alendronate prescription and record protocol adherence. After the initial visit, information regarding Alendronate prescription and administration, concomitant medication use, and non-serious and serious ADRs will be obtained during monthly clinical visits and recorded for up to approximately 6 months after completion of the study, a period that is thought appropriate to document ADRs and serious ADRs.

7. SELECTION AND ENROLLMENT OF SUBJECTS

Inclusion criteria:

- Postmenopausal women who are diagnosed with osteoporosis either by a DXA scan with a T score <-2.5 either by suffering a low intensity fracture (even in the absence of a DXA scan with T score <-2.5). The bone location that will be used in this study – lumbar spine- is among the recommended for evaluation of BMD by bone densitometry.
- Written informed consent

Exclusion criteria:

- Previous treatment with drugs that modify bone metabolism
- Renal failure (GFR <35 ml/min, as suggested by drug spc)
- History of reflux esophagitis, gastric or duodenal ulcers, gastrectomy

- Bone disease such as primary hyperparathyroidism, hyperthyroidism, Paget disease, Cushing syndrome, multiple myeloma, rheumatoid arthritis, or osteogenesis imperfecta.

Enrollment:

Patient pool will comprise of all patients attending the orthopaedic clinic of Larisa Public Hospital. The first 512 patients assessed in this clinic and recommended based on national guidelines and international good clinical practice that they need to be treated with biphosphonates, will be candidates to be enrolled in this study. All patients must sign the appropriate consent form before being enrolled into the study.

8. TREATMENT PROCEDURES AND STUDY PROCEDURES

This study is designed to follow and observe patients who will initiate treatment with Alendronate 70mg in routine clinical practice. No study-specific treatment will be provided and no additional clinical procedures or assessments will be required as part of this observational study. Patients will be observed for a period of up to 12 months after their entry in the study unless patients discontinue the study or are lost to follow up. Information regarding the clinical management of the patients receiving Alendronate 70mg may be collected whenever available, even after treatment discontinuation.

There are no procedures or changes to routine clinical management of patients. It is anticipated that patients will return to the clinic every month to receive their Alendronate 70mg prescription. Patients will be followed for approximately 6 months after their last visit. Available clinical information obtained for routine clinical practice (including those already recorded on the patient medical records ie, baseline characteristics) will be recorded, including Alendronate 70mg administration, previous and current therapies, medical history (including fracture history), ADRs and serious ADRs and co-morbidities.

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate routine clinical care including calcium and vitamin D supplementation, which will be recorded.

9. REMOVAL AND REPLACEMENT OF PATIENTS

Removal of Patients:

Patients have the right to withdraw fully from the study at any time and for any reason without prejudice to her future medical care by the physician or at the institution. Withdrawal of full consent for this study means that the patient does not wish to or is unable to continue further study participation; patient data up to withdrawal of consent will be included in the analysis of the study. The investigator will discuss with the patient appropriate procedures for withdrawal from the study. Should a patient (or a legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable eCRFs.

Replacement of Patients:

Participants who withdraw from the study or lost to follow-up will not be replaced.

10. STATISTICAL CONSIDERATIONS

Study Outcomes:

The following outcomes are to characterize/estimate the effectiveness during the first 12 months of treatment with Alendronate.

Primary outcome:

- BMD change (%) at lumbar spine at 6,12 months of treatment measured by DXA

Secondary outcomes:

- the proportion of patients with severe osteoporosis experiencing one or more new vertebral and non-vertebral fragility fractures assessed by spine radiographs regardless of symptoms
- Compliance to therapy, self-reported by patients
- Days lost from work due to fracture-related back pain, self reported by patients

The following secondary outcomes are to characterize the safety of patients during the first 12 months of treatment with Alendronate and during the 6 month follow up period:

- the proportion of patients with ADR to Alendronate
- the proportion of patients with serious ADR to Alendronate

The Full Analysis Set will consist of all enrolled patients satisfying the inclusion/exclusion criteria that receive at least 46 doses - 96% of the 48 that ideally would receive during the study duration- and have a non-missing enrollment date. All analyses will be performed on this analysis set.

Subsets and/or Covariates:

The following variables will be collected at baseline, either directly as part of routine clinical practice, or from medical records when available:

Demographic patient data:

- Educational level
- Patient employment status
- Patient living situation (at home with spouse/family, at home with care/support, at home alone, nursing home)

Medical condition regarding osteoporosis:

- Body mass index (≤ 25 or > 25 kg/m2)
- Age at menopause
- Cause of menopause (natural onset, clinically/surgically induced)
- Height loss since maximal height
- Height loss in centimeters (cm)
- Previous fracture
    - Previous hip fracture
    - Previous vertebral fracture
    - Other previous fractures
- Previous hospitalization for osteoporotic fracture and/or surgical osteoporotic fracture treatment
- One or more falls experienced during the past 12 months
- One or more episodes of immobility experienced during the past 12 months
- Parent fractured hip
- Current smoker
- Former smoker
- Systemic glucocorticoid use
- Secondary osteoporosis
- Alcohol consumption
- Femoral neck BMD T-score
- Lumbar spine BMD T-score
- Total hip BMD T-score

Patient-related:

- Age (years)
- Age group (< 65, ≥ 65 to <75, ≥ 75 years)
- Time since Post Menopausal Osteoporosis (PMO) diagnosis
- Number of comorbidities
- Any chronic medical condition
- Type of chronic medical condition (diabetes/osteoporosis/hypertension/other)

Sample Size:

A review of published data highlighted that BMD change at lumbar spine at 12 months for postmenopausal women on alendronate 70mg weekly ranges from 3.7%-5.1%.[13-15]

Taking into account the most unfavourable result, which is 5.1%, we will estimate the sample size of our study. We will conduct an observational study which intends to investigate the Lumbar Spine BMD (%) change from baseline to 12 months (single proportion).

Published data estimate that Lumbar Spine BMD increases 5.1% from baseline to 12 months.

We would like to ensure that 95% CI of the Lumbar Spine BMD change (%) is estimated with precision ±2% (i.e. with a margin of error of 2%).

The required sample size would be $n \geq \frac{z^2}{\delta^2} p(1-p) \rightarrow n \geq \frac{1.96^2}{0.02^2} 0.051(1-0.051) \rightarrow n \geq 465$

If we add 10% to compensate for potential loss of subjects, the final number will sum up to n≥ 512 patients.

Thus in order to have sufficient precision and compensate for potential loss of subjects the final sample size should be 512 patients.

Data Analyses

This is an observational study for which the analysis will be descriptive in nature and no formal hypothesis will be tested. T test will be used to assess the change in BMD between baseline and end of study measurements. Significance was indicated at $P < 0.05$.

For quantitative parameters (BMD, days lost from work) mean, standard deviation, median, range (minimum and maximum), as well as number of missing data (if relevant) will be displayed. For qualitative parameters (bone fractures) counts, percentages and number of missing data if relevant will be displayed. Treatment compliance for each patient will be calculated as the number of doses study drug was actually taken, with the maximum count being 48. Compliance will be regarded as a quantitative parameter.

In general, missing values will remain as missing, i.e., no attempt will be made to impute missing values and only observed values will be used in data analyses and presentations.

Baseline characteristics will be described. Demographics, medical history and other baseline variables will be summarized as appropriate to the type of data.

11. SAFETY DATA SELECTION AND ADVERSE EXPERIENCE REPORTING

Adverse Drug Reaction

Definition of Adverse Drug Reaction: An Adverse Drug Reaction (ADR) is defined as an adverse event associated with a given medication at normal dosage. The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study, and involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event. The Investigator should specify the date of onset, intensity, action taken with respect to Alendronate, corrective treatment/therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the Adverse Event was caused by Alendronate.

Lab, vital signs, or ECG abnormalities are to be recorded as adverse events only if they are medically relevant: symptomatic, require corrective treatment, lead to study drug discontinuation and/or fulfill a seriousness criterion. In that case the procedure imposed by the event of a serious adverse drug reaction (SADR) should be followed.

Reporting Procedures for Adverse Drug Reactions: The investigator is responsible for ensuring that all ADRs to Alendronate 70mg observed by the investigator or reported by the patient that occur after the first administration of Alendronate through the end of study and through the following 6 months are captured. The investigator must assess whether any adverse event is possibly related to Alendronate 70mg and if that is the case he should proceed by recording the ADR and assign the following ADR attributes:

- ADR diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Date(s) of onset and resolution,
- Severity, and
- Action taken.

Serious Adverse Drug Reaction

Definition of Serious Adverse Drug Reaction: A SADR is a serious adverse event that is considered related to the medicinal product. A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay). If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

Reporting Procedures for Serious Adverse Drug Reaction: The investigator is responsible for ensuring that all SADRs related to Alendronate 70mg from the beginning of the study until the end of it and during the 6 month follow up period are recorded in the patient's medical record and are reported to a SADR report form. Information provided on the SADR form must be consistent with that recorded on the applicable eCRF (eg, Adverse Drug Reaction Summary eCRF). SADRs will be reported as required to National Organization for Medicines (EOF), in compliance with all reporting requirements according to local regulations for observational studies.

12. REGULATORY OBLIGATIONS

Informed consent:

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial, including the written information given approval/favorable opinion by the Institutional Review Board/Ethics Committee of both the hospital where the study will take place and the Ethical Committee (EC) of the Ministry of Health of Greece. Prior to a patient's participation in the study, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or by

the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

Institutional Review Board/Independent Ethics Committee (IRB/EC):

The Investigator must submit this Study Protocol to the appropriate IRB/EC, and is required to forward to the Sponsor a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/EC composition. The study number, study Protocol title and version number, the documents reviewed (study Protocol, Informed Consent Form, Investigator's Brochure, Investigator's CV, etc.) and the date of the review should be clearly stated on the written IRB/EC approval/favorable opinion. The investigator should notify the IEC/IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports recorded.

All updates to the Investigator's Brochure will be sent to the IRB/EC. If requested, a progress report will be sent to the IRB/EC 6 months after the initiation of the study and a summary of the study's outcome at the end and after the 6 month follow up period of the study.

Patient Confidentiality:

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the site will be identified only by the Study Identification Number (SID) to maintain patient confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SIDs only. Clinical information will not be released without written permission of the patient, except as necessary for monitoring by IRB.

13. ADMINISTRATIVE AND LEGAL OBLIGATIONS

The investigators are responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of observational studies. All investigators will have access to patient medical records and other study-related records needed to verify the entries on the eCRFs where applicable per local governing law and/or regulations.

The investigator is responsible to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

Publication policy:

Presentation and/or publication of the results of the study, using checked and validated data in order to ensure the accuracy of the results is highly encouraged. All investigators must participate sufficiently and contribute in any parts of conception, design, data collection/analysis, drafting of article, critical review of the article to be qualified as authors. All authors should have a copy of the presentation/publication prior to its release and approve it.

14. SUPPLEMENTARY MATERIAL

Data collected per visit

Timing / **Data collection**	**Enrollment**	**Observation period**	**End of Study** (12 months)	**Follow-up period** (6 months)
Informed Consent	X			
Demographics	X			
Patient-related conditions	X			
Medical History	X			
Prior and Current Medication Use	X	X	X	
Menopause History	X			
Alendronate Prescription	X	X	X	
Calcium and Vitamin D supplementation	X	X	X	
ADR	X	X	X	X
SADR	X	X	X	X
Discontonuation and Reasons for Discontinuation	X	X	X	

15. REFERENCES

1. Osteoporosis Clinical guideline for prevention and treatment, Executive Summary, November 2014. http://www.shef.ac.uk/NOGG/NOGG_Executive_Summary.pdf (accessed 20 August 2015)

2. Reginster JY, Burlet N. Osteoporosis: a still increasing prevalence. *Bone* 2006; **38:** S4-9.

3. Dennison E, Mohamed MA, Cooper C. Epidemiology of osteoporosis. *Rheum Dis Clin North Am* 2006; **32:** 617-629.

4. Baccaro LF, Conde DM, Costa-Paiva L, Pinto-Neto AM. The epidemiology and management of postmenopausal osteoporosis: a viewpoint from Brazil. *Clin Interv Aging* 2015; **10:** 583-91.

5. Bliuc D, Alarkawi D, Nguyen TV, Eisman JA, Center JR. Risk of subsequent fractures and mortality in elderly women and men with fragility fractures with and without osteoporotic bone density: the Dubbo Osteoporosis Epidemiology Study. *J Bone Miner Res* 2015; **30:** 637-46.

6. Clinician's Guide to prevention and treatment of osteoporosis. National Osteoporosis Foundation, 2014. http://nof.org/files/nof/public/content/file/2791/upload/919.pdf (accessed 22 August 2015)

7. Papapoulos S, Makras P. Selection of antiresorptive or anabolic treatments for postmenopausal osteoporosis. *Nat Clin Pract Endocrinol Metab* 2008; **4:** 514-523.

8. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009; **361:** 756-765.

9. Body JJ, Bergmann P, Boonen S, et al. Non-pharmacological management of osteoporosis: a consensus of the Belgian Bone Club. *Osteoporosis Int* 2011; **22:** 2769-88.

10. Reyes C, Hitz M, Prieto-Alhambra D, Abrahamsen B. Risks and benefits of bisphosphonate therapies. *J Cell Biochem* 2015; epub ahead of print. DOI: 10.1002/jcb.25266

11. Azuma Y, Sato H, Oue Y, et al. Alendronate distributed on bone surfaces inhibits osteoclastic bone resorption in vitro and in experimental hypercalcemia models. *Bone* 1995; **16:** 235-45.

12. Cranney A, Wells G, Willan A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. *Endocr Rev* 2002; **23:** 508-16.

13. Schnitzer T, Bone HG, Crepaldi G, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Alendronate Once-Weekly Study Group. *Aging (Milano)* 2000; **12:** 1-12.

14. Rosen CJ, Hochberg MC, Bonnick SL, et al. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. *J Bone Miner Res* 2005; **20:** 141-51.

15. Hosking D, Adami S, Felsenberg D, et al. Comparison of change in bone resorption and bone mineral density with once-weekly alendronate and daily risedronate: a randomised, placebo-controlled study. *Curr Med Res Opin* 2003; **19:** 383-94.