CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020560/S012

MEDICAL REVIEW(S)

Memorandum
June 16,1999
To: the file NDA 20-560 Supplement/012 (new indication for the treatment of corticosteroid induced osteoporosis)
From: Solomon Sobel M.D., Director, Division of Metabolic and Endocrine Drug Products /S/ [redacted] 6/16/99
Subject: Approval of Supplement

This supplement was initially submitted on May 26, 1998 and found approvable. The approvable letter asked for further evaluation based on a fully auditted and analyzed data accrued in the extension trial. The original study followed patients for one year and the extension trial increased the time of observation on a subset of patients to 2 years. (The subset of patients in the 2nd year extension trial had characteristics similar to the patients who did not participate in the extension trial). The need for this additional period of study was, among other reasons, to establish more fully the outcome in respect to the fracture incidence in the appendicular skeletion (the non-vertebral, non-rib fracture rate).There was a small trend to an increase in that type of fracture in the first year of study. There are several considerations which arose during our review.

1. What is the optimal time in relationship to the initiation of corticosteroid therapy to give alendronate to prevent fractures?

2. Is there a dose of corticosteroids which is likely to result in decrease in bone mineral density and subsequent fractures?

3. Is there a detrimental effect on appendicular bones that will result from alendronate treatment for corticosteroid induced osteoporosis?

4.What other factors that may contribute to the osteoporosis seen with corticosteroids should one consider before initiating alendronate therapy?

5. Does correction of these factors obviate the need for the administration of alendronate?

6. For how long will alendronate exert a beneficial effect on the reduction of bone mineral density loss?

7. What restrictions should appear in the labeled indication for use in the treatment corticosteroid induced fractures?

8. What phase 4 commitments will we require to further define the usefulness of alendronate in the treatment of corticosteroid induced osteoporosis?

9.What studies should we request in respect to the pediatric population?

10. Is there a different "T" score threshold for fractures induced by corticosteroids. (It has been postulated that corticosteroid treated patients experience fractures at higher bone mineral densities than patient with post-menopausal osteoporosis).

11. What was the median T score for patients in the NDA studies for corticosteroid osteoporosis?

12. When were the majority of fractures experienced in relationship to the start of alendronate therapy?

13. Are the fracture incidences, both vertebral and non-vertebral, unusually low in the NDA studies.

14. Does the effect of corticosteroids on the gastric mucosa make it more vulnerable to ulceration by alendronate than in patients who are not receiving corticosteroids such as a non-steroid treated patient with post-menopausal osteoporosis?

Discussion of the above issues:
1.The NDA studies did not provide an answer to the question of whether alendronate is a preventive agent.
There were very few truly naive patients in respect to corticosteroid treatment. In the analysis, three strata of patients were identified in respect to the use of corticosteroids before the intitiation of alendronate. Stratum 1 was called "newly treated" patients but in fact contained patients who could have had 4 months of treatment with corticosteroids. Since bone loss with corticosteroids is very rapid in the first 6 months of treatment, this group would fail as a good test for preventive qualities of alendronate.In any event, there were too few patients in this stratum to provide adequate evidence for benefit even if we were ot permit a more liberal definition of "newly treated".
The other 2 strata, the intermediate and chronic, included patients who had considerable exposure to corticosteroids before the initiation of alendronate. Thus, there was no clear delineation of a preventive effect. Therefore, we are permitting only a treatment indication.

2. The dose which was studied in the NDA trials was about 7.5 mg of prednisone daily (or its equivalent). We do not know from the NDA trials whether there is a linear osteoporotic effect at lower doses or whether there is a threshold dose in respect to fractures. Therefore , the indication is limited to patients receiving 7.5 mg daily dose of prednisone or higher.

3.In the first year of study, although small in numbers, there was a greater nummber of appendicular fractures in the alendronate group. There was some concern that this might indicate a detrimental effect on cortical bone.
However, at month 24 the cumulative number of patients who experienced non-vertebral fractures was 6/61 (9.8%)in the placebo group and 8/147 (5.4 %) in the alendronate group.

4.Other factors which may contribute to osteoporosis in patients taking corticosteroids are vitamin D and calcium nutritional inadequacy. It is believed that Vitamin D and calcium when given in adequate doses may prevent, to a great degree, the loss of bone in corticosteroid treatment.
Also, estrogen and testosterone deficiency will contribute to osteoporosis. These deficiencies may be present in patients before the start of corticosteroid therapy or may be induced or worsened by such therapy.

5. Correction of hormonal deficencies (if they exist) and improvement of the nutritional status (if poor) in respect to vitamin D and calcium may be beneficial in reducing to a large degree the bone loss associated with corticosteroid therapy.

6. In the NDA studies most of the beneficial effect in respect to bone mineral density was seen in the first year of administration of alendronate. This effect flatttened considerably but was maintained in the 2nd year of therapy. It is not known if continued administration of alendronate is necessary to maintain the effects in the 2nd year. [redacted]

7. We believe that the data are useful for a treatment indication; the prevention indication was not granted because of inadequate data for patients in whom primary prevention was achieved.
We also will limit the indication to patients receiving a daily prednisone dose of 7.5 mg or above. We have recommended that only patients with an initial bone mineral density T score of worse than negative 1.2 be treated. Treatment beyond 2 years is not recommended because this has not been studied.

8. As described above we are requesting studies to explore the necessity of giving maintenance doses of alendronate.

9. The sponsor and we will be discussing pediatric studies.

10. There has been some discussion in the medical literature that fracture vulnerability may be greater at better T scores (than in post-menopausal osteoporosis).
However, there is no certainty in respect to this conjecture.

11. The median T scores in the NDA studies at the start of therapy with alendronate was negative 1.2. There were very few fractures seen in these studies.

12. The majority of the fractures were seen in the first year of the study.

13. The fracture incidence was very low in both the placebo and alendronate groups. We do not have good historical data to compare to this finding.

14. It does not appear that corticosteroids plus alendronate poses a problem of increased ulceration of the gastrointestinal tract.
However, there was "an increase in non-serious upper gastrointestinal adverse experiences seen with the 10 mg dose, due mostly to increases in reports of abdominal pain and acid regurgitation".

Conclusion:
The Division has concluded that an approval may be granted at this time for a treatment indication in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5mg or greater of prednisone and who have low bone mineral density.
Dr. Troendle, the primary medical reviewer, had previously recommended non-approval but with the clear delineation of the indication in respect to treatment (and not prevention) she now favors approval.(see her note of June 16, 1999).

/S/

-Solomon Sobel

APPEARS THIS WAY ON ORIGINAL

CC: Arch NDA 20-560/S-012
HFD-510
HFD-510/SSobel/GTroendle/RHedin

Addendum to MOR
NDA 20560
Merck
Alendronate
16 June 1999

This drug offers some benefit to a minority of the patients who take it for glucocorticoid-induced osteoporosis. The benefit is in preventing bone mineral loss as measured by DXA. The difference between drug and placebo was statistically significant.
By morphometric analysis of spinal X-rays, there were 8 (6.0%) placebo, and 8 (2.4%) Alendronate patients with vertebral fractures; by semiquantitative analysis there were 5 (8.3%) placebo and 2 (1.4%) Alendronate patients. The protocol listed 24 secondary endpoints, of which this was one. The difference was statistically significant.
In spite of the improved bone density and the reduced spinal fracture incidence, stature loss was not prevented.
Although very severe gastrointestinal (principally esophageal and gastric) adverse events have been reported in patients taking Alendronate, they are uncommon, and less severe in the clinical trials. Also, the incidence in these trials is similar in drug and placebo patients.
Total fractures are fewer in the Alendronate group, primarily due to vertebral and rib fractures, with some (not statistically significant) increase in fractures other than vertebral and rib.

Because there is benefit to some patients, and toxicities are not common, the drug can be approved for patients who must stay on glucocorticoids for a prolonged time and who have lost a substantial amount of bone density.

/S/ [redacted]

6/16/99

GT

Alendronate Label

I did not realize what was happening in our conversation with Merck yesterday. The indication, without mention of bone density or any factors for identifying patients with or at high risk of osteoporosis, clearly and simply says that Alendronate is for anyone taking glucocorticoids. No wonder they were not after a prevention indication. I think that 1.2 SD below the mean of premenopausal women for identifying glucocorticoid-induced osteoporosis is, in fact, giving an indication for prevention, because, as far as I know, our definition of osteoporosis in other situations has eroded only from 2.5 to 2 SD. Only if osteoporosis is inevitable when glucocorticoids are given should treatment of all glucocorticoid users be warranted.

The Merck extension studies.

Rate is number of with fractures per 100 women per 2 years.

	Placebo N = 59		Alendronate N = 147		
	Number	Rate	Number	Rate	Number prevented
Vertebral fractures	10	16.9	15	10.2	6.7
Non vertebral fractures	10	16.9	17	11.6	5.3
Rib only fractures	6	10.2	2	1.4	8.8
Non-vertebral, non-rib Fx	4	6.8	15	10.2	-3.4

The number of subjects with fractures that were prevented by Alendronate per 100 subjects per 2 years is 12, of which, 6.7 are vertebral, and 8.8 are rib. The excess of subjects with non-vertebral, non-rib fractures is 3.4 subjects per 200 patient years. Perhaps the excess of non-vertebral, non-rib fractures is offset by the rib fractures, which are painful. And I'm sure we cannot completely discount the vertebral fractures, but together with the difficulty identifying vertebral fractures, it is hard to accept the promotion of this as a drug everyone needs when they go onto glucocorticoid therapy.

I know these numbers are not as precise as I have pretended they are, but they are all we have. Put together with the lack of effect on stature, which is a primary clinical manifestation of spinal fractures, it indicates very small returns for the inconvenience and the cost and risks of taking this drug.

The proposal for phase 4 is almost nothing. There were 51-59 subjects in the 5 and 10 mg and placebo groups in the extension study, of whom some were off glucocorticoids so that the per-protocol analysis had 30-38 subjects per group. For them to take a history of the interval since study's end and do BMD is not going to give much information. On the other hand, I believe their story about how difficult it is to keep the patients on glucocorticoids. It means to me that they did not need treatment, because BMD is restored when glucocorticoids are withdrawn, according to some published articles. Not in those who are postmenopausal, of course, but they should be treated as cases of PMO if that is the case. Actually, I do not know what would be feasible and would get answers to some of the questions. I think the principal thing that would help me to feel better about this drug would be some way to say to the patients that the drug promises very little benefit unless they have a high risk and expect to take the glucocorticoids for a long time. The risk of non-vertebral fractures from this condition is about 6 per 100 patients/year, and there is no benefit relative to stature.

ISI [redacted]

6/16/99

Algiop93
NDA 20560/S012

1 Medical Officer's Review of Response to Approvable Letter

Merck

NDA 20560-012

Generic name: Alendronate sodium tablets

Trade name: Fosamax

Submitted 11/26/97. Action letter, Approvable depending on further safety information 5/26/98.

The core of this response is the report of the 12-month Extension study which followed the 48-week Original study, and the Clinical Review of this follow up is included in this review of the entire response.

Alendronate is effective at preventing further bone loss in patients with Glucocorticoid-induced osteoporosis.
Alendronate has not been shown to reduce the risk of non-vertebral, non-rib fractures.
Alendronate has not been shown to decrease or prevent loss of stature.
Alendronate has been shown to be irritating to the esophagus and to increase the incidence of gastric and esophageal events.

Alendronate should not be approved for treatment of Glucocorticoid-induced osteoporosis.NA

/S/ [redacted]

6/14/99

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APPEARS THIS WAY ON ORIGINAL

NDA 20560
Merck & Co., Inc.
Alendronate Sodium Tablets (Fosamax)
Review completed 6/9/99

This submission was received by the Agency December 16, 1998. It is a response to the Agency's May 26, 1998 Approvable letter. Additional information as, requested in the Approvable letter, is included. Volume 1 of this submission contains an overview of this response. Seven attachments to the Overview of the response constitute the completed Clinical Study Report of the extension studies of alendronate in Glucocorticoid–Induced Osteoporosis (GIOP) and additional safety reviews. I have not reviewed attachment 4, which is an electronic data set for statistical review. Attachments 1 (volume 2), 2 (volumes 3, 4, 5), 3 (volume 6), and 7 (volume 14) contain the report of the extension study of the glucocorticoid-induced osteoporosis studies. Attachments 5 (volumes 8 to 11) and 6 (volumes 12 and 13) contain the special safety reports. The attachments are:

Attachment 1 Copy of the label revised for marketing alendronate for GIOP
Attachment 2 The basic Study report
Attachment 3 Case report forms
Attachment 4 electronic data set
Attachment 5 5-year CIOMS II report: worldwide postmarketing experience with Fosamax
Attachment 6 Review: safety information from Merck osteoporosis trials since filing11/26/97
Attachment 7 Case report tabulations

An electronic submission for clinical review includes Attachments 1, 2, 3, and 7 for Acrobat. This is what I used primarily for the review of those attachments.

FDA specifically requested:

1. patient-months of treatment, **V12P22T3, V12P22T3**
2. drop-out rates, **T24 T25**
3. numbers who remain at risk at the end of two years, **T24,T25,T26,T27,T28**
4. fracture results in terms of patient-months of therapy, **T6**Vertfx **T53, T54,T55,**
5. subgroup analyses indicating interaction between underlying disease and bone density or fractures, **T10, T11,T12,T17,T47** NVFx **p137 to T64**
6. the contribution to efficacy of results from postmenopausal women, who are and are not on hormone replacement therapy, premenopausal women, and men, **T46,T56**
7. all available safety information, including studies that were still ongoing at the time of the NDA submission **Attachments 5 and 6**
8. tables comparing adverse reactions at the time of submission with current information, **Attachment 6, Comprehensive Review of Alendronate Safety in Clinical Trials**
9. retabulation of dropouts identifying those that are new and any changes. **T24,T25,T28**
10. case report forms for all deaths.

Abbreviations Used in this Review:

AE	Adverse Event
BMD	Bone mineral density
BSAP	Bone specific alkaline phosphatase
CF	Clinical Fracture
CFS	Clinical Fracture Study (part of FIT)
Chg or chg	Change
CI	Confidence Intervals
CIO	Corticoiod-Induced Osteoporosis
CO	Combined Osteoporotic Cohort
DXA	Dual Energy X-ray absorptiometry
EG	**Extension GIOP study**
ERB	European Review Board
EX user	Not on glucocorticoids for 4 consecutive weeks
FN	Femoral neck of hip
FX	Fracture
GI	Gastrointestinal
GIOP or GIO	Glucocorticoid-induced osteoporosis
HRT	**Hormone Replacement Therapy**
ITT	Intention to Treat Analysis
IRB	Institutional Review Board
LD	Low dose user - User of less than 7.5 mg glucocorticoid
LS	Lumbar spine
MN	**Multinational GIOP study (082)**
Mo 1	Month 1, baseline of OG
Mo 12	Month 12, baseline of EG at end of OG
Mo 24	End of EG
N or n	Number of subjects
NTx	Urine N-telopeptide crosslinks
OCF	Osteoporotic Clinical Fracture Cohort
OG	Original GIOP studies for NDA (MN + US)
P or p	Probability
Pbo	Placebo
PD	Protocol dose of glucocorticoid (>7.5 mg/day)
PMO	Postmenopausal osteoporosis
PUB	Peptic Ulcer Bleed
RR	Relative Risk
SD	Standard deviation
TB	Total Body
Tr	Trochanter – segment of hip
TH	Total hip
T-score	Standard deviation below that of normal pre-menopausal women
US	United States GIOP study (083)
VF	Vertebral Fracture Cohort
VFS	Vertebral Fracture Study

25 OH D Blood storage form of Vitamin D

3 Material Reviewed : Proposed Draft Labeling, revised to provide for an indication for glucocorticoid-induced osteoporosis.

4 **Chemistry/Manufacturing/Controls**: Alendronate was approved in 1995 to be marketed for postmenopausal osteoporosis (5 and 10 mg/d) and for Paget's Disease(40 mg/d). It is taken orally once daily, and is supplied in tablets of 5, 10, and 40 mg. Chemistry has been reviewed, and will be similar for this indication (5 and 10 mg/d). In addition to Alendronate, the tablets contain microcrystalline cellulose,anhydrous lactose, croscarmellose sodium, and magnesium stearate.

6 Pharmacology/Toxicology: Previously reviewed and found not to be remarkable for toxicity.

7 Clinical Background

6.1 Human Experience: Alendronate was approved in 1995 and has been marketed for about 4 years. Numerous reports of GI adverse events have been reported to FDA, many of them serious. The world-wide and domestic experience have been submitted, as part of this response to the Approvable Letter.

6.2 Foreign Experience: Reported in this submission. Review follows.

6.3 Pharmacokinetics, Pharmacodynamics: Less than 1% absorbed from GI tract

6.4 Directions for Use: Patients are instructed to take with water only after arising in the morning and before taking anything but water by mouth. They are further instructed to remain upright standing or sitting and taking only water by mouth for at least 30 minutes after taking the Alendronate.

7. Clinical Data Sources

7.1 Current Submission: The material submitted in this response to the Approvable Letter, including the review of the Extension study, the safety reports, domestic and foreign, and the proposed label.

7.2 Rationale for use of Alendronate in GIOP

The submission states that it is well accepted that the basic problem in GIOP is excessive osteoclastic bone resorption relative to osteoblastic bone formation, which is responsible for the bone loss. Also, decreased calcium absorption and renal tubular reabsorption of calcium lead to hyperparathyroidism, which increases both resorption and formation. Another factor is the gonadal hormone deficiency and myopathy, which leads to weakness, inactivity, and immobilization bone loss. All of these factors result in increased resorption and "normal" formation.

NOTE: Osteoclast suppression is imposed by addition of Alendronate onto bone already hampered by glucocorticoid suppression of osteoblasts. Because of coupling to the reduced resorption rate, the "normal" formation is only "normal" for the rate of turnover, but reduced relative to normal rates. Osteoblasts are suppressed by glucocorticoids, resulting in direct and indirect suppression, and in suppression of both components of bone turnover.

The submission also says that glucocorticoid therapy has been reported to result in a doubling of the fracture rate and a near tripling of hip fractures; glucocorticoid therapy results in fractures at a higher BMD than in patients with involutional osteoporosis.

NOTE: This dissociation of BMD and fracture rate seems to indicate that there are other factors in the pathogenesis of the osteoporosis associated with glucocorticoid therapy. It is not a condition that parallels postmenopausal osteoporosis.

8Clinical GIOP Extension Study

The first 48 weeks of this study were reviewed prior to the Approvable letter. The first year of treatment was defined as 48 weeks, and the second year consisted of 12 months, a total of 23 months. The protocol for this study was very similar to those for the original GIOP studies (OG). This extension report is the result of pooling two almost identical studies, a multinational study (MN) conducted mostly in Europe and a United States study (US) that together formed the OG. In MN there were 4 groups, treated with placebo or 2.5, 5, or 10 mg Alendronate; in US there were 3 groups, treated with placebo or 5 or 10 mg Alendronate. In the extension GIOP study (EG) of the MN, the dose of the 2.5 mg group was changed to 10 mg daily.

NOTE: References to relevant tables are given throughout this review. The references consist of a T and a number (T10) in 14 point Bold. The tables are numbered as they appear in the electronic report (Adobe Acrobat). **Table 1**, etc is used (Table is written out), the reference is to tables in and made for this review.

8.1 Protocol

8.1.1 Design

Patients who completed MN and US were eligible to enter this extension study (EX). They continued to receive their original dose except the group that was on 2.5 in MN was put on10 mg in EX. The double blind was continued from the original studies.

The 12-month glucocorticoid-induced osteoporosis (GIOP) EX, like the original 48-week GIOP study (OG), was double-blind, placebo-controlled, multicenter, and used multiple doses. The two original studies, MN (multinational) and US (United States), were identical except that MN had a 2.5-mg arm and US had only 5 and 10 mg groups. MN and US were combined into the EX study. Patients formerly on 2.5 mg Alendronate were switched to 10 mg/d. Patients randomized to MN and US of OG were 17-83 years of age, on at least 7.5 mg/d of prednisone or equivalent and expected to require that amount of glucocorticoid for another year. The primary endpoint was bone mineral density (BMD). Some patients were off drug for up to 3 months between the two studies, because of delays in obtaining IRB or ERB approvals.

8.1.2 Proposed Indication: "Treatment and prevention of glucocorticoid-induced osteoporosis in men and women."

8.1.3 Population

8.1.3.1 Inclusions: Patients were admitted to the study if they:

1) completed the last (7th) visit of the original study;
2) were on an oral glucocorticoid dose equivalent to at least 7.5 mg/d prednisone;
3) a) if postmenopausal, were amenorrheic at least 6 months, and,
   b) if on HRT, were on same dose for 6 months and would continue at same dose;
   c) if premenopausal, agreed to practice acceptable birth control;
   d) if male receiving testosterone replacement, had been on the same dose at least 6 months and would continue the same dose;
4) would take the calcium and vitamin D; and
5) understood the risks and procedures of the study.

8.1.3.2 Exclusions:

Patients were excluded if they
1) were incapable of giving consent,
2) might become pregnant,
3) expected to discontinue or alter HRT,
4) were using or had used fluoride or bisphosphonate,
5) were using anticoagulants, calcitonin, deflazacort, cloprednol, calcitriol, alfacalcidol, or any investigational drug.

8.1.4 Methods

Generally, throughout this review, methodology is not described in detail. Most of what description is given is here rather than where the results of the particular evaluation are given.

Visits were scheduled at screening and months 0,1, 3, 6, 9, 12, 18, and 24. Complete schedule of tests is in T4. Patients were required to keep daily record of their glucocorticoid intake.

Estrogen or testosterone change of therapy during the study, caused the patient to be considered a protocol violator, but the patient continued on therapy in the study.

Histomorphology was done at month 12 only in consenting patients. Densitometry and biochemical markers were done at each visit, except that densitometry was not done at visit 1. Data for vertebrae that were fractured at baseline or during the study were not included in the BMD analyses throughout the entire study.

Adverse experiences, pregnancy test, bone-specific alkaline phosphatase (BSAP), N-telopeptides (Ntx), densitometry were assessed at each visit.

Phalangeal bone mineral density was performed to evaluate the utility of this technology.

Hand radiographs in rheumatoid arthritis patients were measured, because it was thought that bisphosphonates may be effective in preventing joint erosions.

Stature Height and weight were measured at months 3, 6, 9, 12, 18, and 24.

Height was assessed by Harpenden stadiometers, Seritex, Carlstadt NJ.

Incident vertebral fractures were primarily determined by computerized digitization and verified by Genant semiquantitative reading.

Spine and hip densitometry were done routinely and total body was determined where available.

Hologic and Lunar densitometers were used, and Medical Data Management, Waltham, MA served as central quality control and analysis center.

Baseline NTx, BSAP, calcium, phosphate and total serum alkaline phosphatase were not different between treatment groups.

Ntx and BSAP were done at [redacted].

Baseline renal function was assessed by serum creatinine.

8.1.5 Endpoints/Objectives/Hypotheses

8.1.5.1 Primary efficacy endpoint:

Percent change in Lumbar Spine (LS) BMD from baseline to last visit patient was PD (protocol dose at least 7.5 mg prednisone or equivalent glucocorticoid) user.

"Hypothesis: Oral alendronate 5 or 10 mg/day only for up to 24 months in all patients requiring long-term use of oral glucocorticoids at doses of 7.5 mg/day oral prednisone or equivalent, will increase lumbar spine BMD by dual-energy x-ray absorptiometry (DXA) relative to similar placebo-treated control patients and preserve (no significant loss) spine BMD by DXA relative to baseline."

8.1.5.2 Secondary efficacy endpoints

a) BMD and fractures
- ✓ LS BMD in patients with entry T-score<-1,
- ✓ femoral neck, trochanter, total hip, and total body BMD,
- ✓ total body and total hip BMD in patients with T-score <-1,
- ✓ incident vertebral fractures: digitized measurements, and semiquantitative evaluation,
- ✓ Femoral neck, trochanter, total hip and total body BMD for percent change from baseline to last time they were PD users.

"Hypothesis: Oral alendronate 5 or 10 mg/day only for up to 24 months in all patients requiring long-term use of oral glucocorticoids at doses of 7.5 mg/day oral prednisone or equivalent, will increase hip and total body BMD by DXA relative to placebo-treated control patients."

b) markers and minerals
- ✓ biochemical markers (urine NTx, total and bone specific alkaline phosphatase),
- ✓ mineral homeostasis by serum calcium and phosphate,

c) relationships of changes in spine BMD to demographic factors
- ✓ glucocorticoid use during and prior to alendronate,
- ✓ disease category,
- ✓ gender, menopausal status,
- ✓ baseline BMD,
- ✓ age, race, height, weight,
- ✓ renal function
- ✓ other medications in patients on placebo and those on alendronate.

"Hypothesis: Oral alendronate 5 or 10 mg/day only for up to 24 months in patients requiring long-term use of oral glucocorticoids at doses of >7.5 mg/day oral prednisone or equivalent and with baseline lumbar spine T-score <-1, will increase (statistically significant difference) spine, hip and total body BMD by DXA both relative to placebo-treated control patients and relative to baseline."

8.1.5.3 Secondary safety objectives:

To define the safety and tolerability profile, using these endpoints:
- ✓ frequency of adverse experiences,
- ✓ frequency of laboratory values out of predefined limits for prespecified parameters,
- ✓ laboratory and vital sign change from baseline,
- ✓ use of concomitant medications.

"Hypothesis: Oral alendronate 5 or 10 mg/day only for up to 24 months will be sufficiently safe and well tolerated to be used in the treatment and prevention of glucocorticoid-induced osteoporosis."