CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-762

MEDICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: April 7, 2005

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-762
Fosamax Plus D (alendronate sodium/cholecalciferol)
Merck

SUBJECT: NDA review issues and recommended action

Background

Dr. Colman has summarized the regulatory history of Fosamax and of the proposed Fosamax Plus D drug product. Briefly, Fosamax was approved in October 2000 for the treatment of osteoporosis in postmenopausal women and to increase bone mass in men with osteoporosis. In the clinical trials of Fosamax (as for all osteoporosis therapies considered by FDA) patients are to receive (per protocol) adequate calcium and vitamin D (generally consisting of approximately 1 gram of elemental calcium daily and at least 400 international units of vitamin D daily). The labeling for Fosamax has always recommended that patients "receive supplemental calcium and vitamin D, if dietary intake is inadequate." In practical terms, this constitutes a recommendation that all patients receive these supplements, and such is accepted clinical practice, though it is far from universally implemented. A drug product containing both alendronate and vitamin D3 is, therefore, a rational combination drug product not only as a combination of convenience but also to address significant non-compliance with recommendations to take vitamin D with alendronate.

In March 2002, in response to a meeting request to discuss their proposal for a fixed-dose, once-weekly combination tablet of alendronate 70 mg and cholecalciferol (vitamin D3) 2800 IU, the Division issued a letter answering the sponsor's questions on the regulatory and scientific/clinical path forward for such a product. At that time, we agreed that a bioequivalence study to establish that no PK interactions existed between alendronate and cholecalciferol would suffice to support the clinical use of the product. We also agreed that this was not a combination drug product, but rather the combination of a drug and a dietary supplement.

Merck's application was submitted on 24 May 2004 and included the results of study 226, the BA/BE study requested. As part of a safety update to the application, Merck submitted the results of study 227, a 15-week, randomized, double-blind, double-dummy trial comparing the effects of the combination product and alendronate 70 mg alone on a number of clinical laboratory parameters.

Issues raised in review

1. Status of the product

> During the review of the application, the conclusion was reached, after internal discussion, discussion with the Office of Medical Policy, and discussion with the Office of Chief Counsel, that this product is in fact a combination drug product.

The term "drug" is defined in § 201(g)(1) the Federal Food, Drug, and Cosmetic Act (the Act) as including "(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man. . .; (D), articles intended for use as a component of any articles specified in clause . . . (B)." Here, the alendronate sodium is indisputably an "article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man," and the vitamin D is clearly "intended for use as a component of" the proposed alendronate sodium drug product. Accordingly, the vitamin D3 in this combination drug product is itself a drug and is regulated as such.

Because this product is a fixed dose combination drug product, it is subject to the combination policy at 21 C.F.R. § 300.50. Of note, 300.50(a) states:

> Two of more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. . . .

The Division has concluded that these standards are met with the proposed product and supported by the current application. With specific regard to labeling, Merck had proposed to label the product to include [redacted] This claim is not acceptable to FDA, given our position (as discussed below) that the vitamin D3 in this product is intended to contribute to the treatment of osteoporosis. Instead, the Agency feels that the labeled indications for this product should be no different than for the original Fosamax and that the standard that must be met is whether the vitamin D3 makes a contribution to this claim. The Division is comfortable that it does (see below). Merck has agreed to this.

2. Combination of alendronate sodium and vitamin D3

As discussed by Dr. Colman, the Division's position is that the vitamin D3 in this product addresses an aspect of the pathophysiology of osteoporosis that is not addressed (indeed could be exacerbated) by alendronate. Specifically, Dr. Colman refers to published literature supporting the efficacy and safety of vitamin D as a treatment to increase BMD and to reduce the risk for osteoporotic fractures in men and women. Mechanistically speaking, vitamin D supplementation, by promoting intestinal calcium absorption as well as by directly suppressing PTH synthesis and secretion by the parathyroid glands, acts to suppress bone mineral loss by a mechanism independent of alendronate's (reduction in bone turnover by inhibition of osteoclast function). More specifically, by its action to inhibit calcium release from bone stores,

alendronate and other bisphosphonates can cause hypocalcemia and thus stimulate PTH release, with potential adverse effects on bone. Addition of vitamin D (and calcium) to the therapeutic regimen in patients treated with bisphosphonates therefore directly addresses an undesirable potential secondary effect of these agents. Thus, as required by § 300.50, the vitamin D contributes to the claimed effects of this combination drug product. Additionally, study 226 establishes that neither the alendronate sodium's nor the vitamin D's bioavailability is affected by the presence of the other in the combination.

In sum, Fosamax Plus D is a rational combination insofar as all patients currently prescribed alendronate also should be taking vitamin D. Thus, there is a significant population "requiring such concurrent therapy." Furthermore, there is ample evidence from literature and based on pathophysiology and biochemistry, and supported by studies of the bioavailability of the active ingredients in the sponsor's product, that each component makes a contribution to the claimed effects (i.e., as stated in the labeled indications) of the combination.

2. Dose of vitamin D3 in the combination

According to the sponsor, the choice of 2800 IU vitamin D3 in this combination is based on current recommendations directing 400 IU vitamin D as "adequate" daily intake for individuals between ages 50 and 70 years. Through extensive internal discussions, review of literature, and discussion with the sponsor, it is acknowledged by all that while this dose is "adequate" for maintaining vitamin D status in the "sufficient" range (and thus theoretically preventing osteomalacia) in most people, it is clearly not universally adequate even for this purpose nor, perhaps more importantly, necessarily adequate as an optimal adjunct in the treatment of osteoporosis. Indeed, given that recommendations for dose requirements are likely to change based on changes in the science with regard to the role of vitamin D in osteoporosis prevention and treatment, at this time it is not practical to expect or require that such a product provide a full, optimal, universally applicable dose of vitamin D to all patients who might be treated with it. Suffice it to say that the sponsor has provided information that over 30% of patients taking alendronate take no vitamin D supplements (despite the labeled recommendation to do so and despite the fact that all evidence supporting the efficacy of alendronate comes from studies in which patients also received vitamin D and calcium supplements). Given this information, at the very least, patients treated with Fosamax Plus D will be absolutely assured of getting, patient by patient, at least the minimum effective (and certainly safe—that is, posing no risk for vitamin D toxicity) amount of vitamin D recommended in current clinical guidelines. As discussed further below, labeling will inform that certain patients may require additional supplementation.

In part addressing the adequacy of the 2800 IU per week dose contained in the proposed product, as noted above, the sponsor submitted the results of study 227 in the 120-day safety update to the NDA. This was a 15-week, randomized, double-dummy, trial of alendronate 70 mg weekly (n=357) vs. alendronate 70 mg/cholecalciferol 2800 IU (n=360) in post-menopausal women examining effects of the two treatment regimens on clinical laboratory parameters. Patients were stratified by baseline 25OHD level (with the cutpoint at 15 ng/mL). The primary endpoint was the proportion of patients with 25OHD levels < 15 ng/mL at week 15. Also examined were

effects on markers of bone turnover, serum calcium concentrations, 24-hour urinary calcium excretion, serum phosphate concentrations, and serum iPTH concentrations.

The average baseline 25OHD concentration across the treatment groups was 22 ng/mL. At week 15, 11% and 32%, respectively, of alendronate/vitamin D patients and alendronate patients had 25OHD serum concentrations < 15 ng/dL. Approximately 2% and 12%, respectively, of alendronate/vitamin D patients and alendronate patients had 25OHD serum concentrations of < 9 ng/mL. Finally, the small difference between treatment groups in the changes from baseline in serum calcium concentrations was consistent with an effect of vitamin D to moderate the effects of alendronate to lower serum calcium. Likewise, the group receiving alendronate/vitamin D showed substantially smaller mean decreases in serum phosphate concentrations. Perhaps most notably in support of an effect of vitamin D as a contributor to the efficacy of the combination (by moderating the hyperparathyroid effects of alendronate) is the finding of mean increases in PTH concentrations of 14% vs. 24%, respectively, in the alendronate/vitamin D vs. alendronate groups.

Dr. Colman and Dr. Kehoe have raised questions about the differences with regard to changes from baseline in 25OHD concentrations observed in study 227 as compared to published studies referenced in Merck's submission. In seeking to explain these differences, it is not possible formally to exclude either differences in the actual quantities of vitamin D administered in the various published studies (we have no data to confirm either the drug content or bioavailability of the formulations used in the other trials) or differences that might result from once weekly versus once daily administration of vitamin D. That said, there are multiple other differences between Merck's study and the study by Chel, et. al., with which its results contrast perhaps most markedly, as discussed by Dr. Colman. These differences include size (45 nursing home residents studied by Chel vs. over 700 patients in the Merck study), age distribution/patient heterogeneity (Chel's were all nursing home residents), and single site (Chel) versus multiple centers worldwide (Merck). In addition, Merck points out that its study was enrolled in the autumn and was conducted therefore across the winter months, at a time when vitamin D synthesis via the effect of UVB on the skin declines markedly, thus apparently reducing the effect of vitamin D supplementation. Dr. Colman has also queried whether taking vitamin D without food (specifically without fat), as necessarily occurs when taking in the combination (since alendronate is supposed to be taken with water only and at least one hour before breakfast), might reduce absorption and thereby result in lesser effects on 25OHD concentrations compared to patients taking vitamin D without regard to meals. In the absence of information on controls on timing of vitamin D administration in the various studies, this question remains formally unanswerable for the time being. Of note, however, is that the Tmax for vitamin D is about 10-12 hours with the Fosamax Plus D product, suggesting that most of the vitamin D is absorbed after breakfast (and therefore at least in part in the context of meals, whether fatty or otherwise).

In sum, the choice of the 2800 IU dose of cholecalciferol contained in the Fosamax Plus D product is based upon current recommendations for adequate daily intake. Evidence has been provided that this dose is indeed adequate to maintain serum concentrations of vitamin D in the vast majority of patients, thereby meeting the requirement of § 300.50 that the dosage of this component be effective for a significant patient population requiring such concurrent therapy.

Additionally, referring to the discussion above on the role of vitamin D as an adjunct to bisphosphonates in the therapy of osteoporosis, the data demonstrating the sufficiency of the dose for a large population permit a conclusion that the vitamin D3 in this proposed product makes a "contribution" to the claimed effects of the combination. That said, insofar as recommendations are likely to change as the science in this area advances, given that individual patient needs are known to vary considerably with season, and that needs differ substantially from patient to patient, it must be emphasized that this product cannot, is not, and ought not be expected to provide a "one-size-fits-all" dose of cholecalciferol for patients who are candidates for alendronate therapy.

Finally, in order to render a more versatile or broadly applicable product, with regard to the vitamin D content, Merck has agreed to develop a fixed-dose combination containing alendronate 70 mg and — vitamin D3 for once weekly administration.

Biopharmaceutics
OCPB has reviewed the biopharmaceutics package and finds it acceptable pending final labeling as recommended and with the following recommendations for phase 4:

1. Sponsor should develop an acceptable vitamin D in vitro dissolution method and acceptance criteria.

Chemistry
ONDC finds the CMC information acceptable and recommends approval. The environmental assessment was waived.

Toxicology
No issues

Labeling
To be negotiated.

Conclusions
In summary, this product is a rational combination drug product, in which each of the components makes a contribution to the effects of the combination, and in which the dosages contained in the combination render a safe and effective treatment for the populations in which it is indicated. The population appropriate for therapy with Fosamax Plus D is the entire population for which Fosamax alone is indicated. This is, therefore, a "significant" population. As above, the availability of such a combination arguably addresses, in part, the significant non-compliance with recommendations to take vitamin D with alendronate (as it would if combined with other bisphosphonates). Additionally, while it is clear that neither this dose nor any dose or array of doses of cholecalciferol combined with alendronate 70 mg could address the vitamin D needs of all patients for whom physicians might prescribe the combination, it is also clear that the 2800 IU weekly dose is a rational, safe, and effective dose for a very large population. In order to make clear that this is not a "one-size-fits-all" product, labeling will state in several places that Fosamax Plus D is not for vitamin D replacement in patients with frank vitamin D deficiency, that certain patients at risk for vitamin D deficiency because of age, debility, confinement (e.g., to a nursing home) should receive additional vitamin D, and that patients with

gastrointestinal malabsorption syndromes may require higher doses of vitamin D and should potentially have their vitamin D status monitored. Finally, Merck has agreed to a phase 4 commitment to conduct studies adequate to support approval of a dosage strength of Fosamax Plus D containing — daily) vitamin D, thereby rendering a product that will more broadly address vitamin D requirements in the indicated populations.

Recommendation

Approve with phase 4 commitment to develop dosage strength containing — vitamin D3.

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/s/

David Orloff
4/7/05 12:38:32 PM
MEDICAL OFFICER

MEDICAL TEAM LEADER MEMORANDUM

NDA: 21-762

DRUG: Alendronate 70 mg/Vitamin D_3 2800 IU, once-weekly

INDICATION: Treatment of postmenopausal and male osteoporosis

COMPANY: Merck

DATE SUBMITTED: 24 May 2004

PRIMARY MEDICAL REVIEWER: Theresa Kehoe, MD

DATE OF MEMO: 23 March 2005

I. BACKGROUND

Pre-NDA Submission

The once-weekly 70 mg alendronate tablet was approved in October 2000 for the treatment of osteoporosis in postmenopausal women and the treatment to increase bone mass in men with osteoporosis.

The Dosing and Administration section of the currently approved labeling for alendronate recommends that patients "receive supplemental calcium and vitamin D, if dietary intake is inadequate."

In March 2002, Merck requested a meeting with the Division to discuss their development plans for a combination tablet containing 70 mg once-weekly alendronate and 2800 IU cholecalciferol (vitamin D_3). The Division denied the meeting request and sent the company the following responses to their questions regarding the regulatory requirements for submission of a NDA for the combination of alendronate + vitamin D:

Clinical

1. We agree that an appropriate bioequivalence study will be sufficient to submit a supplemental NDA for the combination of alendronate and vitamin D. However, we believe that the pharmacokinetic parameters of vitamin D in addition to those of alendronate require investigation.
2. Final wording for the labeling will be determined after review of the appropriate data.
3. We agree that 21 CFR 300.50 does not apply to the combination of alendronate and vitamin D. Further, we agree that you will not be required to conduct

additional clinical trials prior to submission of a supplemental NDA for the combination of alendronate and vitamin D.

4. We agree that you will not be required to conduct preclinical pharmacology, toxicology, or carcinogenicity studies prior to submission of a supplemental NDA for the combination of alendronate and vitamin D.

Biopharmaceutics

1. We recommend a three-way, crossover, randomized, bioequivalence study of three treatment groups: alendronate 70 mg; vitamin D 2800 IU; and alendronate + vitamin D.
2. Pharmacokinetic data should be gathered for both alendronate and vitamin D in all treatment groups.
3. The number of subjects in each treatment group should be prespecified. You should predefine the probability of demonstrating 80% bioequivalence. Please do not add more subjects as the study progresses in order to pass the confidence interval test for bioequivalence.
4. Clarify whether this study will use the currently approved alendronate 70 mg tablet, and the combination alendronate 70 mg and vitamin D 2800 IU tablet, proposed for marketing.

On 24 May 2004, Merck submitted a NDA for the combination of once-weekly 70 mg alendronate and 2800 IU vitamin D_3 and requested approval for the 1) Treatment of osteoporosis in postmenopausal women
2) Treatment to increase bone mass in men with osteoporosis

The NDA included, among other things, the results of study 226, an open-label, crossover study evaluating the bioequivalence of the 70 mg alendronate/2800 IU vitamin D tablet to a 70 mg alendronate tablet, and a 2800 IU vitamin D tablet.

Post-NDA Submissions and Regulatory Activity

During discussions following submission of the alendronate/vitamin D NDA, it became clear that FDA lawyers believed that the combination of alendronate plus vitamin D would be considered a drug, not a drug plus a dietary supplement. This decision changed the approach to the NDA and required us to answer two questions: 1) Since the combination is a drug, would Merck be required to provide evidence to satisfy the requirements of the combination drug regulation, 300.50? and 2) As a drug, what should the Indications and Usage section say about the vitamin D portion of the combination?

As for the drug combination regulations, Merck's claim that they do not have to adhere to these requirements is based in large part on their belief that the vitamin D component of their product is a dietary supplement, not a drug, and therefore 300.50 does not apply. The company also claims that the vitamin D is included in the combination tablet to prevent the development of osteomalacia. Thus, vitamin D is included to "treat" a disease or condition other than osteoporosis, the target disease for which alendronate is currently

approved. However, because the combination of alendronate plus vitamin D is going to be regulated as a drug, and the vitamin D component of the product does play a role in the pathophysiology of osteoporosis (through effects on serum calcium and PTH), not just osteomalacia, Merck's reasoning does not hold up.

As discussed below, there are ample data from published literature to support the efficacy and safety of vitamin D as a therapy to increase bone mineral density and reduce the risk for fracture in men and women with osteoporosis. Moreover, there is evidence that vitamin D and alendronate favorably affect skeletal function through different mechanisms (decrease iPTH levels and inhibit osteoclasts, respectively) and therefore the two drugs make independent contributions to the claimed effects of increasing bone mineral density and decreasing fracture risk of the 70 mg alendronate plus 2800 IU vitamin D combination product. In so doing, the regulatory requirements of the fixed-combination drug regulations are satisfied.

Regarding the question about the appropriate language for the Indications and Usage section of the combination product labeling, Merck has proposed —

Since the combination of alendronate with vitamin D is going to be regulated as a drug, the proposed — is not appropriate.

Instead, Agency lawyers recommend that the indications for use of the 70 mg alendronate plus 2800 IU vitamin D product remain the same as the indications for the currently approved 70 mg alendronate alone product, which are: The treatment of postmenopausal osteoporosis and treatment to increase bone mass in men with osteoporosis. This approach is consistent with the data that indicate that both the alendronate and the vitamin D are contributing to the claimed effects of the combination to treat postmenopausal osteoporosis and increase bone mass in men with osteoporosis.

II. Data Merck Submitted for Review

At the time of submission, the NDA included the results of the definitive relative bioavailability study, 226. After the NDA was filed, Merck submitted, as part of the 120-day safety update, data from study 227, a 15-week, randomized, double-blind, placebo-controlled trial which evaluated the effects of 70 mg alendronate/2800 IU vitamin D vs. 70 mg alendronate alone on a variety of clinical chemistry parameters. Brief review of these studies follows.

Study 226

This was a 2-part, open-label, randomized, 12-week, cross-over study that examined the bioequivalency of the to-be-marketed formulation of 70 mg alendronate + 2800 IU vitamin D, with 70 mg alendronate, and 2800 IU vitamin D. The stated objectives were to compare the urinary excretion of alendronate following administration of a 70 mg

alendronate/2800 IU vitamin D tablet to a 70 mg alendronate tablet (Part I of the study), and to compare the pharmacokinetic parameters (AUC, Cmax) of vitamin D administered as a 70mg alendronate/2800 IU vitamin D vs. 2800 IU vitamin D alone (Part II of the study). A total of 244 healthy adult volunteers took part in the study: 214 in Part I and 30 in Part II. Two-hundred-seven subjects completed Part I of the study and 28 subjects completed Part II. There were slightly more female subjects than males and the ages ranged from 18 to 65 years.

The table below provides the results of the total urinary excretion for alendronate following single doses of 70 mg alendronate/2800 IU vitamin D and 70 mg alendronate alone.

Summary Statistics and GMR With Corresponding 90% Confidence Intervals for Total Urinary Excretion for Alendronate (µg) Following Single-Dose Administration of 70-mg Alendronate/Vitamin D_3 Combination Tablet or 70-mg Alendronate Alone Tablet

Treatment	N	LS† Mean	Median	Min	Max	SD‡	GMR§	90% CI for GMR
Alendronate Total Urinary Excretion (µg)								
Alendronate/ Vitamin D_3	207	197.5	209.8	—		329.1	1.03	(0.91, 1.17)
Alendronate Alone	207	191.9	204.4	—		522.2		

Equivalent amounts of alendronate were excreted in the urine following single doses of alendronate + vitamin D and alendronate alone, indicating that the alendronate is equally bioavailable in the two preparations.

The next table provides the vitamin D concentrations following administration of single doses of 70 mg alendronate + 2800 IU vitamin D and 2800 IU vitamin D alone.

Summary Statistics and GMRs With Corresponding 90% Confidence Intervals for Vitamin D_3 $AUC_{0\text{-}120\ hr}$(ng•hr/mL) and C_{max}(ng/mL) Unadjusted for Endogenous Vitamin D_3Serum Concentrations Following Single-Dose Administration of 70-mg Alendronate/2800-IU Vitamin D_3Combination Tablet or 2800-IU Vitamin D_3 Alone Tablet

Treatment	N	LS† Mean	Median	Min	Max	SD‡	GMR§	90% CI‖for GMR
Vitamin D_3 $AUC_{0\text{-}120\ hr}$ (ng•hr/mL)								
Alendronate/ Vitamin D_3	28	296.4	257.5	—		375.5	0.88	(0.81, 0.95)
Vitamin D_3 Alone	28	337.9	309.6	—		344.2		
Vitamin D_3 C_{max}(ng/mL)								
Alendronate/ Vitamin D_3	28	5.9	5.3	—		3.3	0.89	(0.84, 0.95)
Vitamin D_3 Alone	28	6.6	6.2	—		3.1		

These data indicate that the bioavailability of the vitamin D_3 in the combination tablet is similar to that from the 2800 IU vitamin D tablet.

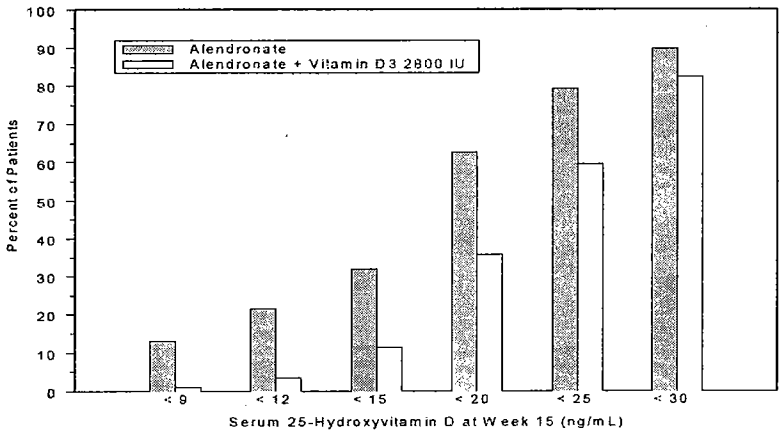
Study 227

This was a randomized, double-blind, active-controlled, 15-week study (with a 24-week extension) to examine the safety and tolerability of 70 mg alendronate plus 2800 IU vitamin D once-weekly vs. 70 mg once-weekly alendronate. A total of 717 subjects, most of whom were postmenopausal women, were randomized 1:1 to either treatment with 70 mg alendronate + 2800 IU vitamin D once-weekly (n=360), or 70 mg alendronate once weekly (n=357). Patients were stratified by baseline level of 25OHD (< 15 ng/ml or ≥ 15 ng/ml). The primary endpoint was the proportion of patients with 25OHD levels < 15 ng/ml at Week 15. Other endpoints included markers of bone turnover, serum calcium levels, 24-hour urine calcium levels, serum phosphate levels, and serum iPTH levels.

A total of 673 subjects, equally divided between groups, completed the 15-week assessment period. The two groups were well-matched for baseline demographic characteristics. Ninety-nine percent were Caucasian, the age range of the participants was 35 to 89 years, and the average baseline lumbar spine BMD T-score was about 0.65. Approximately 22% of the subjects had baseline 25 OHD levels < 15 ng/ml.

The average baseline levels of 25OHD was 22 ng/ml in both treatment groups. At Week 15, 11% of the alendronate + vitamin D subjects vs. 32% of the alendronate alone subjects had 25OHD levels < 15 ng/dl.

The percent of patients in each treatment group with various Week 15 25OHD levels is provided in the following figure.



The mean changes in serum 25OHD levels from baseline to Week 15 were 1.2 ng/ml in the alendronate + vitamin D group and -3.4 ng/ml in the alendronate alone group.

The markers of bone resorption and formation decreased by similar amounts in the two treatment groups (~ 53% for NTx and ~ 26% for alkaline phosphatase).

The mean serum calcium levels decreased by -0.9% and -1.4% in the alendronate + vitamin D and the alendronate alone groups, respectively. The mean serum phosphate levels decreased by -2.4% and -28% in the alendronate + vitamin D and the alendronate alone groups, respectively. The average concentrations of iPTH increased by 14% in the alendronate + vitamin D group and by 24% in the alendronate alone group.

There were no untoward safety issues noted during the conduct of this study.

Comment

In a study by Chel[1], in which 15 nursing home residents with baseline 25OHD levels of 9.0 ng/ml were supplemented with 400 IU daily vitamin D_3 or nothing for 3 months, the mean serum 25OHD levels increased by roughly 15 ng/ml in the treated group and did not change in the control group, such that the absolute average 25OHD level at the end of the trial was 24 ng/ml. By comparison, the relative change in the mean serum 25OHD concentration of 4.5 ng/ml in subjects who received alendronate plus vitamin D vs. those who did not received vitamin D in study 227 was quite small.

Merck argues that the difference between the results of their study and the published study mentioned above is due to differences in baseline levels of 25OHD. In the published study, the average baseline concentrations of 25OHD were below 10 ng/ml; whereas in study 227, the average baseline levels of 25OHD were 22 ng/ml. The company claims, with some justification, that for a given dose of vitamin D, the largest increases in 25OHD levels will be seen in patients with the lowest baseline 25OHD levels.

When one examines the changes in 25OHD levels in the subgroup of 76 patients treated with alendronate + vitamin D who had average baseline 25OHD levels of 12 ng/ml, the levels of 25OHD increased by 4 ng/ml (and decreased by about 2 ng/ml in the alendronate alone group) after 15 weeks of treatment. For the subgroup of patients with an average baseline 25OHD level of 20 ng/ml, the increase in 25OHD was 1.9 ng/ml, and for the subgroup of patients with an average baseline 25OHD level of 32 ng/ml, 25OHD concentrations decreased by 2.2 ng/ml.

So, while the absolute changes in serum 25OHD levels following 15 weeks of supplementation with 2800 IU once-weekly vitamin D were smaller in study 227 than in Chel's study of elderly patients who received 400 IU daily vitamin D for 12 weeks, the patients in study 227 who had the lowest baseline 25OHD levels did have the largest relative increases in 25OHD levels, albeit much smaller increases than those noted in the study by Chel.

There are a number of possible explanations for the different results from study 227 and the study by Chel. Merck's study was conducted in a variety of countries around the

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[1] Chel VGM, Ooms ME, Popp-Snijders C, et al. Ultraviolet irradiation corrects vitamin D deficiency and supppresses secondary hyperparathyroidism in the elderly. *J Bone Miner Res* 1998;13(8):1238-42.

world and included over 700 subjects ranging in age from 35 to 89 years, while the 45 subjects in Chel's study were all from a single nursing home in the Netherlands and ranged in age from approximately 65 to over 90 years. The subjects from the two studies may have had different dietary intakes of vitamin D and calcium and different exposures to ultraviolet-B radiation. Different formulations of vitamin D_3 were used. A daily 400 IU cholecalciferol tablet manufactured by Duphar, from the Netherlands in Chel's study, and a weekly 2800 IU cholecalciferol tablet manufactured by — . It is unknown if the two vitamin D preparations have different potencies. And lastly, since vitamin D is fat-soluble, its absorption from the small intestine is enhanced when co-administered with food that contains fat. It is possible that the larger increases in serum 25OHD levels reported in Chel's vs. Merck's study are due to subjects in the former study taking their daily vitamin supplement with food, whereas subjects in Merck's study took their supplement on an empty stomach.

Since the results of study 226 indicate that the bioavailability of the vitamin D in the alendronate + 2800 IU vitamin D tablet is similar to that from the 2800 IU vitamin D tablet alone, the differences between study 227 and Chel's study are not apparently due to alendronate interfering with the absorption of the vitamin D.

Dr. Kehoe has raised the possibility that the relative bioavailability or the effect of cholecalciferol in repleting or maintaining vitamin D stores may differ when it is consumed on a daily vs. a weekly basis. To the best of my knowledge, no published studies have compared the effects equivalent doses of daily vs. weekly cholecalciferol (or any form of vitamin D) have on serum 25OHD levels. Dr. Kehoe's concern may thus be a legitimate one.

One possible way to answer this question would be to examine the absorption of a given dose of radiolabeled cholecalciferol when administered on a daily basis (e.g., 400 IU) vs. when given as a bolus (e.g., 2800 IU). To simplify things, this could be done in a small animal model such as the rat.

III. Published Data on Vitamin D, Bone Mineral Density, and Fracture Prevention

In 1997, the Institute of Medicine's (IOM) Food and Nutrition Board recommended a dietary reference intake of vitamin D of 400 IU per day for men and women aged 51 to 70 years and 600 IU per day for men and women over the age of 70.

Since these guidelines were issued, there has been considerable debate within the medical community in general and the osteoporosis field in particular regarding the optimal intake of vitamin D, with many experts now suggesting daily intakes far larger than those recommended in the 1997 IOM report.

For example, the authors of a 2002 meta-analysis concluded that 400 – 800 IU daily cholecalciferol may significantly increase bone mineral density and reduce the risk for

osteoporotic fractures[2]. British researchers reported in 2003 that 100,000 IU cholecalciferol taken orally every four months (equivalent to 800 IU/day) for 5 years reduced the risk for fractures from 11.1% to 8.8% in more than 2500 elderly men and women[3]. In a recently published editorial in *Osteoporosis International*, six well-known vitamin D experts concluded that anywhere from 400 to 1600 IU daily cholecalciferol may be required to achieve levels of serum 25OHD and iPTH associated with reductions in fracture risk[4].

Interestingly, a growing body of data support vitamin D's ability to enhance lower extremity function and reduce the risk for falls in older patients[5,6]. This may well be an additional mechanism whereby supplemental vitamin D lowers the risk for osteoporotic fractures.

It is clear that the amount of vitamin D supplementation needed to maximize skeletal function and reduce the risk for fractures varies depending on a person's age, gender, race, dietary intake of vitamin D and calcium, and exposure to sunlight. A "one size fits all" approach to vitamin D supplementation would therefore not be in the best interest of patients taking alendronate for the treatment of osteoporosis.

For this reason, as well as the precedent set by other combination drug products approved by the Agency, I believe Merck should, at a minimum, manufacturer the 70 mg once-weekly dose of alendronate with a — dose of cholecalciferol. This could be done as a phase 4 study.

Regulatory Recommendation

Approve the 70 mg alendronate + 2800 IU cholecalciferol once-weekly tablet with the proviso that Merck agrees to manufacture a 70 mg alendronate + — cholecalciferol once-weekly tablet as a phase 4 commitment.

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[2] Emmanuel Papadimitropoulos, George Wells, Beverley Shea, William Gillespie, Bruce Weaver, Nicole Zytaruk, Ann Cranney, Jonathan Adachi, Peter Tugwell, Robert Josse, Carol Greenwood and Gordon Guyatt , the Osteoporosis Methodology Group, and the Osteoporosis Research Advisory Group. Meta-Analysis of the Efficacy of Vitamin D Treatment in Preventing Osteoporosis in Postmenopausal Women. *Endocrine Reviews* 2002; 23 (4): 560-569.

[3] Daksha P Trivedi, Richard Doll, Kay Tee Khaw. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ 2003; 326: 469.

[4] Bess Dawson-Hughes, Robert P. Heaney, Michael F. Holick, Paul Lips, Pierre J. Meunier and Reinhold Vieth. Estimates of optimal vitamin D status. *Osteoporosis International*. Published online: 18 March 2005.

[5] Bischoff-Ferrari HA, Dietrich T, Orav EJ, Zhang Y, Karlson EW, Dawson-Hughes B. Higher 25-hydroxyvitamin D levels are associated with better lower extremity function in both active and inactive adults 60+ years of age. Am J Clin Nutr 2004; 80:752–758.

[6] Bischoff-Ferrari HA, Dawson-Hughes B, Willett W, Staehlin H, Bazemore M, Zee R, Wong J. Fall prevention by vitamin D treatment: a meta-analysis of randomized controlled trials. J Am Med Assoc 2004; 291:1999–2006.

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CLINICAL REVIEW

Application Type	NDA
Submission Number	21762
Submission Code	N-000-BC
Letter Date	May 23, 2004
Stamp Date	May 24, 2004
PDUFA Goal Date	March 24, 2005
Reviewer Name	Theresa Kehoe, M.D.
Review Completion Date	March 7, 2005
Established Name	Alendronate sodium/vitamin D_3
(Proposed) Trade Name	Fosamax PlusD
Therapeutic Class	bisphosphonate and vitamin D
Applicant	Merck
Priority Designation	S
Formulation	Combination tablet
Dosing Regimen	70mg/2800IU once weekly
Indication	Osteoporosis
Intended Population	postmenopausal women, men

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer believes that the alendronate once weekly combination tablet of 70mg alendronate and 2800IU vitamin D_3 is approvable, contingent upon the fulfillment of the following deficiencies:

- The sponsor should provide evidence of vitamin D's role in osteoporosis treatment and fracture prevention in postmenopausal women and men.
- The sponsor should discuss and provide support for the benefit of combination alendronate/vitamin D_3 therapy compared with alendronate therapy for the treatment of osteoporosis.
- The sponsor should provide an explanation for the suboptimal increases in 25 hydroxyvitamin D levels achieved with the combination alendronate/vitamin D_3 tablet treatment when compared with levels achieved with other vitamin D_3 supplements, as detailed in Table 2.5:1 in the clinical overview section of the NDA submission.
- The sponsor should propose a development plan for combination tablet(s) with doses of vitamin D_3 that provides an adequate dose range which will allow satisfactory 25 hydroxyvitamin D levels to be achieved. The bioequivalence and bioavailability of alendronate will need to be confirmed with any higher vitamin D_3 doses.
- The sponsor should provide the financial disclosure information for Protocol 227.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Merck Research Laboratories, Inc. has submitted this 505b(2) new drug application for alendronate sodium 70mg and cholecalciferol (vitamin D_3) 2800IU combination once weekly tablet, trade name Fosamax PlusD. Alendronate is a member of the bisphosphonate class of medications. Alendronate 70mg once weekly is already indicated for the treatment of osteoporosis in postmenopausal women and to increase bone mass in men with osteoporosis. In addition to alendronate therapy, it is recommended that patients receive supplemental calcium and vitamin D, if dietary intake is inadequate. Vitamin D insufficiency is increasingly recognized as a common problem in older Americans and osteoporosis is a metabolic bone disease that is made worse by inadequate vitamin D. Fosamax PlusD has been developed as a convenience product to combine the approved 70mg alendronate tablet with an amount of vitamin D recommended to maintain bone health. The indications sought in this application include the treatment of osteoporosis in postmenopausal women

and to increase bone mass in men with osteoporosis

In initial discussions regarding development, it was agreed that because vitamin D_3 is a dietary supplement, as well as a natural metabolite, and the intent of the combination tablet was to provide once-weekly nutritional supplementation, the clinical study requirements of 21 CFR 300.50 for the combination of 2 or more drug products should not apply. However, with the evolution of applications under the fixed-combination drug regulations, the Agency's current position is that, in this context, vitamin D_3 should be considered a drug and the clinical study requirements of 21 CFR 300.50 for the combination of 2 or more drug products should apply to the Fosamax/Vitamin D_3 combination tablet. As such, [redacted] is not appropriate and the combination tablet should be evaluated on the basis of the current Fosamax indication - treatment of osteoporosis in postmenopausal women and treatment to increase bone mass in men with osteoporosis.

1.3.2 Efficacy

The bioavailability of the alendronate 70mg once weekly tablet is not appreciably altered by the addition of 2800IU vitamin D_3. The addition of vitamin D_3 may confer a protective effect against the expected decrease in serum calcium and subsequent increase in PTH levels seen with alendronate therapy.

In Protocol 227, after 15 weeks of therapy, the proportion of subjects with insufficient serum 25-hydroxyvitamin D levels (<15 ng/mL) was significantly lower in the combination alendronate/vitamin D_3 group when compared to the alendronate alone group. However, 6% subjects with baseline 25 hydroxyvitamin D levels of 15 – 25 ng/mL and 2% of subjects with baseline levels > 25 ng/mL shifted into the insufficient range despite receiving the alendronate/D_3 combination tablet. As well, in the overall study population the 25 hydroxyvitamin D levels achieved by Week 15 were low. At a time when many experts advocate a 25 hydroxyvitamin D level of 30 ng/mL or above for sufficiency, 61% of subjects in the alendronate/vitamin D_3 combination tablet group had 25 hydroxyvitamin D levels that did not exceed 25ng/mL (compared to 78% in the alendronate only group) while 78% of subjects in the alendronate/vitamin D_3 combination tablet group had 25 hydroxyvitamin D levels less than 30ng/mL (compared to 85% in the alendronate only group). In addition, in subjects with 25 hydroxyvitamin D levels > 25 ng/mL at baseline, there was a decrease in the mean level by Week 15 (-2.2 ng/mL in the alendronate/vitamin D_3 group and -6.1 ng/mL in the alendronate only group).

Though the data submitted indicate that the vitamin D_3 bioavailability for the 70mg alendronate/2800IU vitamin D_3 combination tablet is similar to that for the vitamin D_3 alone tablet, this reviewer has great concern that the dose of vitamin D_3 utilized is insufficient to meet demands and provide adequate vitamin D status. In Merck's present study, Protocol 227, use of the combination tablet with 2800IU vitamin D_3 weekly did not achieve or even maintain optimal 25 hydroxyvitamin D levels in some subjects. The increase achieved with the current combination tablet was +1.2 ng/mL, which is remarkably small compared to other trials of vitamin D_3 supplements (range: +7.4 ng/mL - +15 ng/mL). The current adequate intake of vitamin D set by the Institute of Medicine is 400IU per day for adults age 51-70 years and 600IU per day in adults over age 70 years. Because patients over age 70 years are at high risk of

fracture, they are a population that will be targeted for anti-resorptive therapy. Supplementation with the currently proposed dose of 70mg alendronate/2800IU vitamin D_3 may be insufficient to achieve or maintain optimal 25 hydroxyvitamin D levels in this population. Therefore, higher doses of vitamin D_3 should be investigated.

1.3.3 Safety

The studies submitted with this NDA indicate that the combination alendronate/vitamin D_3 weekly tablet is safe. There were no unexpected safety findings uncovered during the review. There was an imbalance between the alendronate only group and the alendronate/vitamin D_3 group in the number of subjects who withdrew due to laboratory adverse events. All of the withdrawals occurred in the alendronate group and were due to low 25 hydroxyvitamin D levels. This was not unanticipated, due to the lack of vitamin D supplementation in the alendronate only group. and acts to stress the importance of adequate vitamin D nutrition.

The upper limit of normal intake for vitamin D is considered 2000 IU/day. While the vitamin D dosing with the combination alendronate/vitamin D_3 weekly tablet exceeds this amount on the day of dosing, there was no evidence of hypercalcemia or hypercalciuria in study subjects.

1.3.4 Dosing Regimen and Administration

The current dosing guidelines for the alendronate 70mg once weekly tablet were followed in Protocol 227 and should be maintained at the present recommendations. In addition, it is recommended that adequate calcium and vitamin D to ensure nutritional sufficiency be included as part of the regimen for any patient on alendronate therapy. The alendronate/vitamin D_3 combination tablet is being developed for patient convenience with the intent to replace the need for individual vitamin D supplements.

1.3.5 Drug-Drug Interactions

There does not appear to be any untoward interaction between alendronate and cholecalciferol such that the bioavailability of alendronate of vitamin D_3 is altered.

1.3.6 Special Populations

Alendronate 70mg once weekly is currently approved for therapy in postmenopausal women and men with osteoporosis. The efficacy and safety of alendronate are currently being evaluated in a high risk pediatric population with metabolic bone disease.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Merck Research Laboratories, Inc. has submitted this 505b(2) new drug application for alendronate sodium [(4-amino-1- hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate] 70-mg and cholecalciferol, vitamin D_3 [(3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-trien-3-ol] 2800IU combination once weekly tablet, proposed trade name Fosamax PlusD. Alendronate is a member of the bisphosphonate class of medications. This combination product has been developed to help ensure normal vitamin D nutrition in patients for which alendronate 70-mg once weekly is already indicated for the treatment of osteoporosis. Indications sought include treatment of osteoporosis in postmenopausal women —
— and treatment to increase bone mass in men with osteoporosis —
—

2.2 Currently Available Treatment for Indications

Current medications approved for the treatment of postmenopausal osteoporosis include salmon calcitonin (Miacalcin nasal spray), daily and weekly alendronate sodium (Fosamax), daily and weekly risedronate sodium (Actonel), daily ibandronate sodium (Boniva), the selective estrogen receptor modulator raloxifene (Evista), and teriparatide (Forteo).

Current medication available to increase bone mass in men with osteoporosis include daily and weekly alendronate sodium (Fosamax) and teriparatide (Forteo).

Supplemental vitamin D and calcium are the base therapies in the osteoporosis treatment algorithm proposed by the 2004 Surgeon General's report on bone health and osteoporosis[1]. Current products available to help ensure adequate vitamin D nutrition are numerous over-the-counter dietary supplements. One oral vitamin D product is available by prescription - ergocalciferol (Drisdol) which is a vitamin D_2 product and approved for the treatment of hypoparathyroidism, refractory rickets, also known as vitamin D resistant rickets, and familial hypophosphatemia. There are currently no oral prescription vitamin D_3 products in the U.S.

2.3 Availability of Proposed Active Ingredient in the United States

Alendronate sodium is currently available in daily 5mg, 10mg and 40mg tablets, weekly 35mg and 70mg tablets and oral buffered solution. Alendronate 40mg tablet is available for treatment of Paget's Disease of bone. Alendronate sodium 10mg daily was initially approved for the treatment of postmenopausal osteoporosis in September, 1995. Other indications subsequently approved include the prevention of osteoporosis in postmenopausal women (5mg daily dose) in April 1997, the treatment of glucocorticoid-induced osteoporosis in women (5mg daily or 10mg daily for postmenopausal women not on estrogen) and men (5mg daily) receiving glucocorticoids in June 1999. A once weekly tablet formulation (35mg for prevention of

postmenopausal osteoporosis and 70mg for treatment of postmenopausal osteoporosis) was approved in October 2000. Alendronate 10mg daily was approved to increase bone mass in men with osteoporosis in September of 2000. Alendronate 70mg weekly oral buffered solution was approved in August, 2003 as an alternative for those individuals who have difficulty swallowing a tablet or prefer a solution.

Vitamin D_3, is normally obtained by exposure of skin to ultraviolet light and/or diet (including nutritional supplementation). There are numerous dietary supplements with vitamin D_3, either alone, or in combination with calcium or other vitamins. In 1997, the Institute of Medicine set the adequate intake (AI) of vitamin D as 400IU/day for those 51 - 70 years old and 600 IU/day for those over 70 years old[2]. The dose of vitamin D_3 in the 70mg alenrdonate/2800IU vitamin D_3 combination tablet was selected because it provides the same cumulative amount of vitamin D_3 as 7 daily doses of 400IU each, is generally regarded as safe, and should be sufficient to ensure adequate vitamin D in osteoporotic patients, including those whose supplemental requirements may be greater than average.

2.4 Important Issues With Pharmacologically Related Products

Bisphosphonate are used in the prevention and treatment of postmenopausal, and corticosteroid-induced osteoporosis, osteoporosis in men, Paget's disease, hypercalcemia of malignancy, and bony metastases. Safety concerns with oral bisphosphonates include esophageal and gastric irritation and ulceration. Other concerns that have emerged with postmarketing data include the occurrence of eye inflammation, bone pain and osteonecrosis of the jaw. Class labeling for bisphosphonates regarding the use of these drugs in women of childbearing age and the potential for fetal toxicity after remote exposure to the drug has been effected.

Safety concerns with vitamin D preparations include development of hypervitaminosis D and subsequent hypercalcemia, hypercalciuria and associated symptoms including anorexia, nausea, and vomiting, polyuria, polydipsia, weakness, nervousness, and pruritus.

2.5 Presubmission Regulatory Activity

The sponsor sought input from the Agency regarding design aspects of the development program of the drug product as outlined below:

- In a meeting request letter, the sponsor proposed the development of a combination alendronate and vitamin D_3 tablet. The development plan included a study demonstrating the bioequivalence of alendronate between the marketed 70mg tablet and the planned 70mg alendronate/2800IU vitamin D_3 combination tablet to support labeling consisting of the approved indications for the 70mg Fosamax® once weekly tablet, —

—

- In addition, the sponsor requested confirmation that because vitamin D_3 is a dietary supplement, as well as a natural metabolite, and the intent of the combination tablet was to provide once-weekly nutritional supplementation based upon seven times a standard

daily over-the-counter dose of vitamin D_3, the clinical study requirements of 21 CFR 300.50 for the combination of 2 or more drug products should not apply. Merck also requested confirmation that preclinical pharmacology, toxicology, and carcinogenicity studies with vitamin D_3 or the alendronate/vitamin D_3 combination would not be required. The Agency confirmed that an appropriate alendronate bioequivalence study would be sufficient to file an application for the proposed combination tablet in a letter dated March, 11 2002. The Agency also confirmed that 21 CFR 300.50 was not applicable to the combination tablet and that no further clinical trial would be required under this regulation, and that no preclinical pharmacology, toxicology, and carcinogenicity studies would be required.

- An 10-Apr-2002 memo of understanding was generated with subsequent telephone and electronic conversations between the sponsor and the Agency which confirmed that the Agency's primary concern was with the comparison of alendronate bioavailability in the combination with that in the Fosamax® 70mg tablet, but, the definition of the pharmacokinetic parameters of vitamin D_3 was also of interest.

2.6 Other Relevant Background Information

With the evolution of applications under the fixed-combination drug regulations, the Agency's current position is that the clinical study requirements of 21 CFR 300.50 for the combination of 2 or more drug products should apply to the Fosamax/Vitamin D_3 combination tablet. As such, —— is not appropriate and the combination tablet should be evaluated on the basis of the current Fosamax indication - treatment of osteoporosis in postmenopausal women and treatment to increase bone mass in men with osteoporosis.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

3.2 Animal Pharmacology/Toxicology

Please see Dr. Davis-Bruno's review for complete details. Pharmacology/Toxicology data have not been provided or needed for this application since approval is based on the prior decision of safety and efficacy in the approval of Fosamax (alendronate) 70 mg once weekly in Oct. 2000 and Rocaltrol (calcitriol) in 1978.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The goal of the combination tablet development program was to demonstrate alendronate bioequivalence between the 70mg alendronate/2800 IU vitamin D_3 combination tablet and the 70mg alendronate tablet, and to provide pharmacokinetic information for the vitamin D_3 component of the combination tablet. Demonstration of alendronate bioequivalence would allow bridging to existing data describing the efficacy of once-weekly 70mg alendronate for treatment of osteoporosis. Two pilot studies (P183 and P220) were conducted prior to the definitive bioequivalence study. These studies were conducted to ensure that co-administration of vitamin D_3 with alendronate would not adversely affect the bioavailability of alendronate, and to explore the pharmacokinetics of vitamin D_3 using the newly developed sensitive mass spectrometric assay. The definitive bioequivalence study, Protocol 226, investigated both alendronate and vitamin D_3 pharmacokinetics, each in a separate part of the study. All 3 studies were performed in healthy subjects.

In addition, protocol 227 was conducted to evaluate the efficacy of alendronate 70mg/vitamin D_3 2800IU administered once weekly as a combination tablet to reduce the proportion of patients with vitamin D insufficiency (serum 25-hydroxyvitamin D <15 ng/mL) in men and postmenopausal women with osteoporosis, compared to alendronate 70mg alone after 15 weeks of treatment. This study, while submitted in the 4 month safety update, was reviewed in detail for all efficacy and safety outcomes.

4.2 Tables of Clinical Studies

NDA 21762 Studies						
		Subjects enrolled (% compl)	Age years	Population	Study Duration	Primary Endpoint
Clinical Studies						
Protocol 227 P2/3, R, DB	Total	717 (94)	66.8	osteoporotic men and postmenopausal women	15 weeks	reduce the proportion of Vit D insufficiency
	Aln+Vit D_3*	338 (94)	66.6			
	Aln	357 (94)	67.0			
Clinical Pharmacology Studies						
Protocol 226 P2/3,OL, XO	Total	244 (96)	40.8	healthy adult men and women	36hr/session 12d w/o	urinary excretion PK parameters of alendronate, D_3
	Part I	214 (97)	41.6			
	Part II	30 (90)	35.2			
Protocol 220 P2/3,OL, XO	Aln+Vit D_3*	12 (100)	32.5	healthy adult men and women	3 sessions 12d w/o	pilot = estimate bioavailability of aln+vitD vs. aln
	Aln					
	Vit D_3*					
Protocol 183	Aln+Vit D_3*	14 (100)	51	healthy adult	2 sessions	pilot = estimate

NDA 21762 Studies						
		Subjects enrolled (% compl)	Age years	Population	Study Duration	Primary Endpoint
P2/3,OL, XO	Aln only			men and women	14d w/o	bioavailability of aln+vitD vs. aln

* Protocol 183 utilized — Vit D3, all other studies utilized 2800IU Vit D3
P2/3 = Phase 2/3; R = randomized, DB = double-blind; OL = open-label; XO = crossover

4.3 Review Strategy

This review focuses on the clinical study Protocol 227, which was submitted in the 4 month safety update, as well as safety data from Protocol 226. Because of the pilot nature and small amount of subjects enrolled, minimal time was spent in review of Protocols 183 and 220.

4.4 Data Quality and Integrity

The Division of Scientific Investigation (DSI) was consulted for this NDA. The consult focused on Protocol 226, the definitive bioavailability protocol. Following inspections of one clinical study site and the clinical laboratory center, DSI found that the data from Protocol 226 are acceptable.

4.5 Compliance with Good Clinical Practices

All studies appear to have been conducted in accordance with FDA guidelines on "Good Clinical Practice" and the principles of the Declaration of Helsinki.

4.6 Financial Disclosures

Financial disclosure information was provided by the sponsor and reviewed by this reviewer. One investigator for — held equity interest in the sponsor company exceeding $50,000.00. There were four investigators for this — study. It is unlikely that this investigator's financial affected the outcome of this — study and it would not have had an impact on the definitive bioequivalence study. No financial disclosure information is available for Protocol 227, as this study was submitted as a safety update intended for review of safety data only. However, since the efficacy data from this study have contributed to the review of this application, the sponsor will need to supply the financial disclosure information.

5 CLINICAL PHARMACOLOGY

Please see Dr. Lau's review for complete details.

5.1 Pharmacokinetics

Protocol 226 is the definitive study comparing the bioavailability of alendronate in the 70mg alendronate/2800IU vitamin D_3 combination tablet to the 70mg alendronate alone tablet. As

well, this study evaluated the bioavailability of vitamin D_3 in the combination tablet versus the 2800IU vitamin D_3 alone tablet.

The geometric mean ratio for the 36-hour cumulative alendronate urinary excretion of the 70mg alendronate/2800IU vitamin D_3 combination tablet to the 70mg alendronate alone tablet was 1.03 and the 90% CI was 0.91 – 1.17. Based on the cumulative alendronate urinary excretion, the alendronate in 70mg alendronate/2800IU vitamin D_3 combination tablet is equally bioavailable to the 70mg alendronate alone tablet. Bioequivalence could not be adequately assessed because the urine sampling intervals were not short enough to determine the maximum alendronate excretion rate.

The geometric mean ratio for the vitamin D_3 $AUC_{0\text{-}12h}$ (endogenous vitamin D_3 unadjusted) for the 70mg alendronate/2800IU vitamin D_3 combination tablet to the 2800IU vitamin D_3 alone tablet was 0.88 and the 90% CI was 0.81 – 0.95. The geometric mean ratio for the vitamin D_3 C_{max} (endogenous vitamin D_3 unadjusted) for the 70mg alendronate/2800IU vitamin D_3 combination tablet to the 2800IU vitamin D_3 alone tablet was 0.89 and the 90% CI was 0.84 – 0.95. Based on these observations, the vitamin D_3 bioavailability for the 70mg alendronate/2800IU vitamin D_3 combination tablet is similar to that for the vitamin D_3 alone tablet.

The sponsor proposed the same in-vitro dissolution method and acceptance criteria for alendronate in the combination tablet as that to alendronate alone tablet. The sponsor did not propose an in-vitro dissolution method for vitamin D_3 in the combination tablet.

5.2 Pharmacodynamics

No new pharmacodynamic data is included in the bioequivalence studies. Change in markers of bone turnover were secondary efficacy endpoints for Protocol 227 and are discussed in the efficacy section of this review.

5.3 Exposure-Response Relationships

The approved 70mg weekly dose of alendronate was used for the combination tablet. No new exposure response data have been submitted. The dose of vitamin D used in the combination tablet was selected because it represents 7 times the daily dose recommended by the Institute of Medicine for individuals aged 51 to 70, and is also the cumulative weekly equivalent of the daily dose previously used in the alendronate efficacy studies. No data are provided evaluating exposure-response relationships with varying doses of vitamin D_3.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: Treatment of Postmenopausal Osteoporosis

6.1.1 Methods

Protocol 227 is reviewed in depth and evaluated for the evidence that the alendronate/ D_3 combination tablet maintains 25 hydroxyvitamin D levels and decreases the proportion of subjects with vitamin D insufficiency.

6.1.2 General Discussion of Endpoints

For treatment of osteoporosis, fracture reduction remains the primary efficacy parameter. Alendronate 70mg once weekly has previously been shown to be efficacious in the treatment of osteoporosis in postmenopausal women and to increase bone mass in men with osteoporosis. The definitive bioequivalence study, Protocol 226, has shown that the alendronate in 70mg alendronate combination tablet is equally bioavailable to the 70mg alendronate alone tablet. The studies submitted with this application provide no further information for fracture reduction efficacy with vitamin D_3 use. As well, there is no information to suggest that the combination alendronate/vitamin D_3 tablet provides additional benefit over the alendronate tablet for treatment of osteoporosis.

Changes in bone mineral density and bone biomarkers provide supportive evidence of efficacy for treatment of osteoporosis. Secondary endpoints for Protocol 227 include the biochemical markers of bone turnover, urine N- telopeptide of Type 1 collagen corrected for creatinine (NTx) and serum bone-specific alkaline phosphatase (BSAP), which were assessed at screening, Weeks 5, 10 and 15. While this information will help determine if adequate anti-resorptive effect is maintained in the alendronate/vitamin D_3 combination tablet when compared to alendronate alone, it offers no information regarding suppression of bone turnover and increased bone mineral density with vitamin D_3 alone.

The primary objective of Protocol 227 was to evaluate the efficacy of the alendronate/D_3 combination tablet compared to alendronate alone to reduce the proportion of patients with vitamin D insufficiency after 15 weeks of treatment. The primary endpoint was 25-hydroxyvitamin D levels at screening, weeks 5, 10 and 15. This study does not have a vitamin D_3 only arm for which to compare whether alendronate interferes with vitamin D_3 absorption and action.

Of note, Protocol 227 utilized the commercially available — assay for measurement of 25 hydroxyvitamin D levels. In a study conducted to compare results of various vitamin D assays, significant variability was found between the eight laboratories assessed[3]. In this study one laboratory used the HPLC methodology, which is considered the standard. The other laboratories utilized the either the — . RIA methodology (2 labs) or the — CPBA assay (three labs). With the HPLC methodology as the comparative standard, only one other laboratory, which used the — RIA assay, showed similar results. The laboratories using the — assay all significantly overestimated basal concentrations of circulating 25 hydroxyvitamin D and underestimated the exogenously added 25 hydroxyvitamin D levels.

COMMENT: In an effort to provide consistency in reported 25 hydroxyvitamin D levels, all findings have been converted to conventional units (ng/mL) utilizing the conversion

formula of nmol/L divided by 2.496. In addition, all vitamin D dose information has been converted to international units (IU) utilizing the conversion formula of µg times 40.

6.1.3 Study Design

Protocol 227 was a 15-week, randomized, double-blind, multicenter, active-controlled study to assess the safety, tolerability, and efficacy of 70mg alendronate/2800IU vitamin D_3 tablets in men and postmenopausal women with osteoporosis. The alendronate/vitamin D_3 once weekly tablet was evaluated against the 70mg alendronate once weekly marketed tablet. The primary efficacy endpoint was the ability of the alendronate/vitamin D_3 tablet to reduce the proportion of patients with vitamin D insufficiency (serum 25-hydroxyvitamin D <15 ng/mL) compared to alendronate alone after 15 weeks of treatment. Secondary efficacy endpoints included the biochemical markers of bone turnover, urine N- telopeptide of Type 1 collagen corrected for creatinine (NTx) and serum bone-specific alkaline phosphatase (BSAP) which were assessed at screening, Weeks 5, 10 and 15. Parathyroid hormone and serum calcium were assayed in samples collected at screening, Day 1, and Weeks 5, 10, and 15. Urine calcium and creatinine was collected at Visits 2 and 7.

6.1.4 Efficacy Findings

Protocol 227: This protocol enrolled a total of 717 subjects, 682 (95%) were postmenopausal women and 35 (5%) were men. The mean age was 66.8 years. Almost all of the study participants were Caucasian (98.6%). The mean baseline serum 25 hydroxyvitamin D level was 22.4 ± 9.2 ng/mL.

Proportion of Subjects with Vitamin D Insufficiency: As outlined in the table below, the percentage of subjects with insufficient serum 25-hydroxyvitamin D levels (<15 ng/mL) was significantly lower in the alendronate/vitamin D_3 group (11%) when compared to the alendronate alone group (32%) after 15 weeks of therapy ($p<0.001$). The relative risk (alendronate/ vitamin D_3 versus alendronate) was 0.36 ($p<0.001$) with 95% CI of (0.27, 0.48).

Study P227: Proportion of Subjects with Low 25-OH Vitamin D Levels (APT)				
	Aln+VitD		**Aln**	
N	360		357	
N, APT	357		351	
	<15ng/mL	**<9ng/mL**	**<15ng/mL**	**<9ng/mL**
At baseline; n (proportion)	76 (0.21)	0	75 (0.21)	0
At Week 15; n (proportion)	41 (0.11)	4 (0.01)	112 (0.32)	46 (0.13)
Vitamin D < 15 ng/mL				
Relative Risk	0.36			
95% CI	0.27 , 0.48			
p-value	< 0.001			
Vitamin D < 9 ng/mL				
Relative Risk	0.09			
95% CI	0.03 , 0.23			
p-value	< 0.001			

COMMENT: It should be noted that, while no subjects were vitamin D deficient at baseline, 4 (1%) subjects in the alendronate/vitamin D_3 combination tablet group developed levels consistent with vitamin D deficiency (< 9 ng/mL).

Change in Vitamin D Level: As outlined in the table below, baseline 25 hydroxyvitamin D levels were similar between the two treatment groups. Subjects in the alendronate/vitamin D_3 group increased 25 hydroxyvitamin D by 1.2 ng/mL, compared with the alendronate only group which had a decrease in 25 hydroxyvitamin D levels of 3.4 ng/mL. The least-squares mean difference was 4.6 ($p < 0.001$). In the subgroup of patients with vitamin D insufficiency at baseline, the increase in 25 hydroxyvitamin D levels was 3.7 ng/mL in the alendronate/vitamin D_3 group versus a decrease of 1.7 ng/mL in the alendronate alone group. Smaller increases were seen in subjects considered vitamin D sufficient. In fact, subjects with vitamin D levels >25 ng/mL at baseline had decreased levels of 25 hydroxyvitamin D at Week 15. The alendronate/vitamin D_3 group had an absolute change of -2.2 ng/mL versus the alendronate only group with an absolute change of -6.1 ng/mL.

Study P227: 25-OH Vitamin D Level (APT)		
	Aln+VitD	**Aln**
N	**360**	**357**
N, APT	357	351
Vitamin D, baseline ng/mL (±SD)	22.2 ± 9.0	22.1 ± 9.4
Vitamin D, Week 15ng/mL (±SD)	23.1 ± 7.9	18.4 ± 8.7
Absolute Change (95% CI)	1.2 (0.6 , 1.8)	-3.4 (-4.0 , -2.8)
LS Mean Difference	4.6	
95% CI	4.0 , 5.3	
p-value	< 0.001	
Subgroup, Baseline D < 15, n	76	75
Vitamin D, baseline ng/mL (±SD)	12.1 ± 1.7	12.1 ± 1.7
Vitamin D, Week 15ng/mL (±SD)	15.8 ± 3.9	10.4 ± 4.0
Absolute Change (±SD)	3.7 ± 3.7	-1.7 ± 3.4
Subgroup, Baseline D 15 – 25, n	158	166
Vitamin D, baseline ng/mL (±SD)	19.6 ± 2.8	19.6 ± 3.0
Vitamin D, Week 15ng/mL (±SD)	21.5 ± 5.2	16.4 ± 5.4
Absolute Change (±SD)	1.9 ± 4.9	-3.2 ± 4.5
Subgroup, Baseline D > 25, n	123	110
Vitamin D, baseline ng/mL (±SD)	31.7 ± 7.7	32.8 ± 8.6
Vitamin D, Week 15ng/mL (±SD)	29.6 ± 7.6	26.7 ± 8.1
Absolute Change (±SD)	-2.2 ± 5.6	-6.1 ± 5.1

COMMENT: It is concerning that in subjects with 25 hydroxyvitamin D levels > 25ng/mL at baseline, there was a decrease in the mean level by Week 15. Many experts advocate a 25 hydroxyvitamin D level of 30 ng/mL or above for sufficiency. After 15 weeks of therapy, 61% of subjects in the alendronate/vitamin D_3 combination tablet group had 25 hydroxyvitamin D levels that did not exceed 25ng/mL (compared to 78% in the alendronate only group) while 78% of subjects in the alendronate/vitamin D_3 combination tablet group had 25 hydroxyvitamin D levels less than 30ng/mL (compared to 85% in the alendronate only group).

Overall, the 25 hydroxyvitamin D levels achieved by Week 15 appear low when compared to other published studies (see table below). One difficulty in comparing studies with regard to the effect of supplementation on 25 hydroxyvitamin D levels is the complexity of the laboratory measurement itself and the significant variability between laboratory methodologies. That said, the differences are striking. The reason for the differences is not clear. It may be that weekly dosing with this vitamin D_3 product is inadequate.

Effect of Vitamin D_3 Supplementation on 25 Hydroxyvitamin D levels

			25 hydroxyvitamin D level (ng/mL)		
Study	**Age***	**Vitamin D_3 dose**	**baseline**	**follow-up**	**Duration**
Protocol 227	67	2800 weekly	22.2	23.1	15 weeks
Protocol 227**	68	2800 weekly	12.1	15.8	15 weeks
Chel, 1998[4]	85	400 daily	9.2	24	3 months
Lips, 1996[5]	84	400 daily	8	23	3 months
McCauley, 1998[6]	76	400 daily	10	17.4	6 months
Lips, 2001[7]	67	400-600 daily	28.4	37.0	6 months
Lips, 1996[8]	80	400 daily	10.8	24.8	12 months
Peacock, 2000[9]	76	600 daily	24.2	47.6	12 months
Dawson-Hughes, 1997[10]	70	700 daily	28.7	44.8	36 months
Pfiefer, 2001[11]	75	800 daily	10.3	25.9	2 months
Freaney, 1993[12]	74	800 daily	2.4	16.4	1 months
Sebert, 1995[13]	83	800 daily	2.6	14.6	6 months
Chapuy, 1996[14]	86	800 daily	16	40	6 months
Veith, 2001[15]	42	1000 daily	17.3	27.5	5 months
Veith, 2001	40	4000 daily	15.1	38.6	5 months

* mean age in years
** subset of subjects with baseline 25OH D levels < 15ng/mL

Vitamin D Shift Table: As outlined in the table below, when evaluating patients who shifted 25 hydroxyvitamin D status, for subjects in the alendronate/vitamin D_3 group with baseline serum 25 hydroxyvitamin D levels in the insufficient range (<15ng/mL), 62% shifted in the higher ranges (>15 ng/mL). Subjects in the alendronate only group who began with baseline serum 25 hydroxyvitamin D levels in the insufficient range (<15ng/mL), only 16% shifted in the higher ranges (>15 ng/mL). It must also be noted that 4.3% of subjects in the alendronate/vitamin D_3 group who began with sufficient 25 hydroxyvitamin D levels shifted into the insufficient range by Week 15, compared to 17.8% in the alendronate only group.

Study P227: Vitamin D Shift Table (APT)

	Aln+VitD			**Aln**		
N	**360**			**357**		
N, APT	357			351		
Baseline Vitamin D	**Week 15 Vitamin D**			**Week 15 Vitamin D**		
	Total	**< 15**	**> 15**	**Total**	**< 15**	**> 15**
< 15ng/mL	76	29 (38.2)	47 (61.8)	75	63 (84.0)	12 (16.0)
15-25 ng/mL	158	10 (6.3)	148 (93.7)	166	48 (28.9)	118 (71.1)
> 25ng/mL	123	2 (1.6)	121 (95.7)	110	1 (0.9)	109 (99.1)

COMMENT: Overall, 6% subjects with baseline 25 hydroxyvitamin D levels of 15 – 25 ng/mL and 2% of subjects with baseline levels > 25 ng/mL shifted into the insufficient range despite receiving the alendronate/D_3 combination tablet. While the occurrence is clearly lower than what is seen in the alendronate only group, it is a sufficient number to raise concern.

Markers of Calcium Metabolism: The table below outlines the changes seen in markers of calcium metabolism. Alendronate's action as a bone antiresorptive agent has been well described. Serum calcium levels fell in both treatment groups. Although the decrease was smaller in the alendronate/D_3 group the difference was not significant. As well, serum phosphorus levels fell in growth both groups. Parathyroid hormone levels increased in both groups with a statistically significant difference of -10.43 (p= 0.004). Twenty-four-hour urine calcium levels decreased in both groups and there was no significant difference between treatment groups.

Study P227: Markers of Calcium Metabolism (PP)				
	Aln+VitD		**Aln**	
N	**360**		**357**	
N, PP	325		319	
	Baseline	Week 15	Baseline	Week 15
Serum Calcium	9.49	9.43	9.48	9.38
Percent Change	-0.87		-1.38	
Treatment Difference (95% CI)	0.51 (-0.08 , 1.10)			
p-value	0.09			
Serum Phosphate	3.58	3.47	3.61	3.45
Percent Change	-2.37		-3.60	
Treatment Difference (95% CI)	1.22 (-0.64 , 3.09)			
p-value	0.198			
24hour Urine Calcium	172.58	144.19	170.61	132.73
Percent Change	-23.00		-28.41	
Treatment Difference (95% CI)	5.41 (-1.08 , 11.91)			
p-value	0.102			
Parathyroid Hormone	47.35	52.47	45.46	54.65
Percent Change	13.90		24.33	
Treatment Difference (95% CI)	-10.43 (-17.57 , -3.30)			
p-value	0.004			

COMMENT: The changes noted in serum calcium and PTH suggest that the addition of vitamin D_3 in the combination tablet may confer a protective effect against the expected decrease in serum calcium and subsequent increase in PTH level seen with alendronate therapy.

Markers of Bone Metabolism: Bone specific alkaline phosphatase (BSAP) and urinary N-telopeptide (NTx) levels were evaluated to assess bone turnover between the two groups. As outlined in the table below, there was no significant difference between the alendronate/D_3 group and the alendronate group with regard to bone formation (serum osteocalcin -27% in the

alendronate/D_3 group vs. -25% in the alendronate only group) or bone resorption (urinary NTx -53.40% in the alendronate/D_3 group vs. -53.27% in the alendronate only group).

Study P227:Bone Biomarkers (PP)				
	Aln+VitD		**Aln**	
N	**360**		**357**	
N, PP	325		319	
	Baseline	**Week 15**	**Baseline**	**Week 15**
Bone Specific Alkaline Phosphatase	28.29	20.89	28.34	21.60
Percent Change	-27.21		-25.16	
Treatment Difference (95% CI)	-2.06 (-4.91 , 0.80)			
p-value	0.157			
Urinary NTx	62.93	29.97	63.96	30.89
Percent Change	-53.40		-53.27	
Treatment Difference (95% CI)	-0.13 (-3.67 , 3.41)			
p-value	0.942			

6.1.6 Efficacy Conclusions

The effectiveness of decreasing bone turnover, increasing bone density and thus fracture reduction efficacy with 70mg weekly alendronate dosing is well established. The results of Protocol 227 in conjunction with the definitive bioequivalence study Protocol 226, show that the addition of 2800IU vitamin D_3 to the 70mg alendronate tablet does not alter the effectiveness of the weekly alendronate dose.

In Protocol 227, after 15 weeks of therapy, the proportion of subjects with insufficient serum 25-hydroxyvitamin D levels (<15 ng/mL) was significantly lower in the combination alendronate/vitamin D_3 group when compared to the alendronate alone group. However, it must be noted that 1% of subjects in the combination therapy group decreased 25 hydroxyvitamin D levels into the deficient range (<9 ng/mL). The mean change in 25 hydroxyvitamin levels after 15 weeks of therapy was +1.2 ng/mL for the alendronate/vitamin D_3 group and -3.4 ng/mL for the alendronate only group. All subjects with a baseline 25 hydroxyvitamin D level > 25 ng/mL had decreases in 25 hydroxyvitamin D levels (-2.2 ng/mL in the alendronate/vitamin D_3 group and -6.1 ng/mL in the alendronate only group). Overall, after 15 weeks of therapy, 61% of subjects in the alendronate/vitamin D_3 combination tablet group had 25 hydroxyvitamin D levels that did not exceed 25ng/mL (compared to 78% in the alendronate only group) while 78% of subjects in the alendronate/vitamin D_3 combination tablet group had 25 hydroxyvitamin D levels less than 30ng/mL (compared to 85% in the alendronate only group).

The increase in 25 hydroxyvitamin D levels achieved with the weekly 70mg alendronate/2800IU vitamin D_3 seems very small in comparison to other published reports. It may be that weekly dosing with this vitamin D_3 product is inadequate. The reason for this difference needs to be addressed by the sponsor.

Certainly, the smaller decreases seen in serum calcium and PTH levels suggest that the addition of vitamin D_3 in the combination tablet may confer a protective effect against the expected decrease in serum calcium and subsequent increase in PTH level seen with alendronate therapy.

Though data submitted indicate that the vitamin D_3 bioavailability for the 70mg alendronate/2800IU vitamin D_3 combination tablet is similar to that for the vitamin D_3 alone tablet, this reviewer has great concern that the dose of vitamin D_3 utilized is insufficient to meet demands and provide adequate vitamin D status. The current adequate intake of vitamin D set by the Institute of Medicine in 1997 is 400IU per day for adults age 51-70 years and 600IU per day in adults over age 70 years[16]. In Merck's present study, Protocol 227, use of the combination tablet with 2800IU vitamin D_3 weekly did not achieve or even maintain optimal 25 hydroxyvitamin D levels in some subjects. Because patients over age 70 years are at high risk of fracture, they are a population that will be targeted for anti-resorptive therapy. Supplementation with the currently proposed dose of 70mg alendronate/2800IU vitamin D_3 may be insufficient to achieve or maintain optimal 25 hydroxyvitamin D levels. Therefore, higher doses of vitamin D_3 should be investigated.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

No deaths occurred in either Protocol 227 or 226.

7.1.2 Other Serious Adverse Events

In Protocol 227, 22 (3.1%) subjects [7 (1.9%) subjects in the alendronate/vitamin D_3 group and 15 (4.2%) subjects in the alendronate only group] experienced a serious adverse event. As outlined in the table below, most subjects continued in the study after the onset of the SAE. Most of the events listed are not likely to be related to alendronate or vitamin D_3.

Study P227: Serious Adverse Events

Patient	Age	Sex	Event	Onset (day)	Action	Days off drug
Alendronate + D Group						
2159	55	F	pancreatic carcinoma	45	d/c	
2236	71	F	basal cell carcinoma	51	cont	1
2474	68	F	blepharitis / trichiasis	4	cont	3
2332	67	F	depression	36	cont	5
2334	67	F	upper limb fracture	60	cont	3
2500	88	F	traumatic hematoma	65	cont	2
2502	80	F	basal cell carcinoma	63	cont	0
Alendronate only Group						
2020	82	M	thrombosis/ PE	87	cont	2
1034	68	F	syncope/abdo pain/vomiting	2	d/c	
2682	66	F	head injury/contusion/ rib fx	88	cont	3
2694	55	F	retinal detachment	83	cont	4
2469	69	F	gastric ulcer/gastric cancer	73	d/c	

Study P227: Serious Adverse Events						
2246	85	F	anemia	62	cont	2
1317	70	F	anemia	49	cont	6
2366	53	M	tibia/fibula fracture	69	cont	6
2526	70	F	cerebrovascular accident	46	cont	3
1447	66	F	respiratory tract infection	95	cont	3
2484	78	F	squamous cell skin Ca	71	cont	1
2506	82	F	myocardial infraction	55	cont	5
2273	68	F	transient ischemic attack	26	cont	6
1451	82	F	atrial fibrillation	86	cont	1
1326	65	F	bronchopneumonia	60	cont	5

No serious adverse events occurred in Protocol 226.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In protocol 227, 673 (93.8%) subjects completed the study. The most common reason for withdrawal was due to adverse events (discussed below).

In protocol 226, 235 (96.3%) subjects completed the study. Six subjects withdrew consent , one subject discontinued due to an adverse experience (discussed below), two subjects were lost to follow-up and one subject discontinued at poststudy.

7.1.3.2 Adverse events associated with dropouts

In Protocol 227, a total of 35 (4.9%) subjects withdrew from the study due to adverse events. Withdrawals were evenly distributed between the two treatment groups [18(5.0%) subjects in the alendronate/vitamin D_3 group and 17 (4.8%) subjects in the alendronate only group]. As outlined in the table below, gastrointestinal adverse events followed by musculoskeletal adverse events and nervous system adverse events were the most reason for withdrawal in both groups.

Study P227: Adverse Events Leading to Withdrawal			
	Aln+VitD	**Aln**	**Total**
N	360 (%)	357 (%)	717 (%)
Total	18	17	35
Gastrointestinal	8 (2.2)	9 (2.5)	17 (2.4)
Hepatobiliary	0	1 (0.3)	1 (0.1)
Body as a Whole	1 (0.3)	1 (0.3)	2 (0.3)
Infections	1 (0.3)	0	1 (0.1)
Metabolic	1 (0.3)	0	1 (0.1)
Musculoskeletal	3 (0.8)	3 (0.8)	6 (0.8)
Nervous	2 (0.6)	2 (0.6)	4 (0.6)
Neoplasms	1 (0.3)	1 (0.3)	2 (0.3)

Study P227: Adverse Events Leading to Withdrawal			
	Aln+VitD	**Aln**	**Total**
Respiratory	1 (0.3)	0	1 (0.1)
Skin and Subcutaneous	1 (0.3)	1 (0.3)	2 (0.3)
Vascular	1 (0.3)	0	1 (0.1)
The same patient is counted only once in a category, but may appear in more than one category			

In protocol 226, one 25 year-old subject discontinued due to adverse events (chest pain and right shoulder pain) while receiving the 70mg alendronate dose. Cardiac evaluation was normal and no final diagnosis was discovered.

7.1.3.3 Other significant adverse events

No subject required dose alteration due to an adverse event in Protocols 227 or 226.

7.1.4 Other Search Strategies

No special search algorithms were utilized in this safety review.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were assessed continuously during the study at each visit with directed questions and recorded in the case report form.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

An adverse event (AE) was appropriately defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which did not necessarily have to have a causal relationship with the treatment. Pre-existing conditions that worsened during the study were to be reported as adverse events. Serious adverse events were appropriately defined. Adverse events listings utilized MedDRA preferred terms.

7.1.5.3 Incidence of common adverse events

As outlined in the section below, the overall incidence of AEs in Protocol 227 was comparable between the two treatment groups and occurred in 59% of study subjects. The most common adverse event categories were infectious, gastrointestinal and musculoskeletal. The most common clinical adverse events were nasopharyngitis, arthralgia, back pain, and headache.

In Protocol 226, adverse events occurred in a total of 85 subjects [52 (21.8%) in the alendronate/ D_3 combination tablet group, 37 (17.5%) in the alendronate only group and 8 (26.7%) in the vitamin D_3 only group]. The most common adverse event was headache, occurring in 20

subjects while receiving alendronate only, 33 subjects receiving the alendronate/ D_3 combination tablet and 4 subjects receiving vitamin D only.

7.1.5.4 Common adverse event tables

Study P227: Adverse Events			
	Aln+VitD	**Aln**	**Total**
N, safety population	**360**	**357**	**717**
Total subjects with AEs	**215 (59.7)**	**210 (58.8)**	**425 (59.3)**
Body as a whole	20 (5.6)	19 (5.3)	39 (5.4)
Gastrointestinal	62 (17.2)	76 (21.3)	138 (19.2)
Injury*	21 (5.8)	18 (5.0)	39 (5.4)
Nervous	28 (7.8)	20 (5.6)	48 (6.7)
Cardiac	4 (1.1)	8 (2.2)	12 (1.7)
Hepatobiliary	1 (0.3)	1 (0.3)	2 (0.3)
Neoplasms	4 (1.1)	3 (0.8)	7 (1.0)
Respiratory	17 (4.7)	10 (2.8)	27 (3.8)
Endocrine/Metabolic	5 (1.4)	9 (2.5)	14 (2.0)
Musculoskeletal	59 (16.4)	73 (20.4)	132 (18.4)
Infectious	91 (25.3)	76 (21.3)	167 (23.3)
Immune	5 (1.4)	1 (0.3)	6 (0.8)
Blood and Lymphatic	1 (0.3)	4 (1.1)	5 (0.7)
Skin and Appendages	17 (4.7)	18 (5.0)	35 (4.9)
Renal / Urinary Disorders	4 (1.1)	4 (1.1)	8 (1.1)
Reproductive	2 (0.6)	2 (0.6)	4 (0.6)
Vascular Disorders	17 (4.7)	11 (3.1)	28 (3.9)
Eye Disorders	6 (1.7)	13 (3.6)	19 (2.6)
Hearing / Vestibular	6 (1.7)	8 (2.2)	14 (2.0)
Psychiatric	8 (2.2)	10 (2.8)	18 (2.5)
* including fracture The same patient is counted only once in a category, but may appear in more than one category			

7.1.5.5 Identifying common and drug-related adverse events

Based on experience with currently approved oral bisphosphonates, adverse events of special interest that may be related to drug include fracture, gastrointestinal disorders, musculoskeletal pain, eye disorders, and osteonecrosis of the jaw.

Fracture: As outlined in the table below, a total of eight subjects experienced a fracture during protocol 227. All fractures were at nonvertebral sites. As a safety concern, combination alendronate/vitamin D_3 did not alter the occurrence of fractures in this osteoporotic population.

Study P227: Fractures as Adverse Event						
Patient	Age	Sex	Fracture site	Onset (day)	T score	Comment
Alendronate + D Group						
2334	67	F	upper limb fracture (elbow)	60	-2.7	on Ca, T4

Study P227: Fractures as Adverse Event						
1359	63	F	hand fracture	22	-3.3	on Ca + D
2584	83	F	rib fracture	4	-4.0	on Ca + D
2696	57	F	radial fracture	94	-3.3	on Ca, ERT
Alendronate only Group						
2366	53	M	tibia/fibula fracture	69	-3.4	no Ca
2098	54	F	foot fracture	105	-2.5	on Ca
2313	69	F	calcaneus fracture	107	-3.2	on Ca
2682	66	F	rib fracture	88	-1.8	on Ca

Gastrointestinal Adverse Events: Oral, nitrogen-containing bisphosphonates are well known to cause gastroesophageal irritation. In protocol 227, a total of 102 subjects experienced adverse events related to the gastrointestinal tract which may be related to known bisphosphonate effects. The most common adverse events were abdominal pain, dyspepsia and nausea. Event rates were slightly higher in the alendronate only group.

Study P227: Gastrointestinal Adverse Events			
	Aln+VitD	**Aln**	**Total**
N, safety population	**360**	**357**	**717**
Total subjects with AEs	**47**	**55**	**102**
Abdominal pain/discomfort	18 (5.0)	25 (7.0)	43 (6.0)
Diarrhea	7 (1.9)	6 (1.7)	13 (1.8)
Dyspepsia/ GERD	12 (3.3)	15 (4.2)	27 (3.8)
Esophagitis/Esoph erosion	0	2 (0.6)	2 (0.3)
Gastritis	2 (0.6)	3 (0.8)	3 (0.4)
Gastric Ulcer	0	1 (0.3)	1 (0.1)
Gastric disorder, NOS	0	1 (0.3)	1 (0.1)
Nausea	14 (3.9)	11 (3.1)	25 (3.5)
Vomiting	4 (1.1)	7 (2.0)	11 (1.5)

Musculoskeletal Adverse Events: An increased incidence of bony pain, noted primarily in post-marketing, spontaneous adverse event reporting, has been observed with bisphosphonate use. Overall, musculoskeletal pain symptoms occurred in 61 subjects (26 in the alendronate/vitamin D_3 group and 35 in the alendronate only group). Specifically, bone pain occurred in 6 subjects, with a higher incidence in the alendronate only group (5 subjects, compared to 1 subject in the alendronate/vitamin D_3 group).

Study P227: Musculoskeletal Adverse Events			
	Aln+VitD	**Aln**	**Total**
N, safety population	**360**	**357**	**717**
Total subjects	**26**	**35**	**61**
Back pain	15 (4.2)	15 (4.2)	30 (4.2)
Bone pain	1 (0.3)	5 (1.4)	6 (0.8)
Chest wall pain	1 (0.3)	2 (0.6)	3 (0.4)
Musculoskeletal pain	0	1 (0.3)	1 (0.1)

Study P227: Musculoskeletal Adverse Events			
	Aln+VitD	**Aln**	**Total**
Neck pain	5 (1.4)	5 (1.4)	10 (1.4)
Pain in extremity	8 (2.2)	13 (3.6)	21 (2.9)

Eye Adverse Events: An increased incidence of inflammatory eye diseases, such as uveitis and scleritis, has been reported with bisphosphonate use. Overall, 19 [6 (1.7%) subjects in the alendronate/vitamin D_3 group and 13 (3.6%) subjects in the alendronate only group] subjects experienced adverse events related to the eye. Symptoms related to eye inflammation (including pain, erythema, pruritis, conjunctivitis, blepharitis, scleritis and iritis) occurred in 10 subjects. Events are outlined in the table below.

Study P227: Ocular Adverse Event					
Patient	Age	Sex	Event	Onset (day)	Comment
Alendronate + D Group					
2115	71	F	Eye pain	20	
2421	68	F	Eye pruritis	40	
2474	68	F	Blepharitis	4	
2510	71	F	Blepharo-conjunctivitis	54	
Alendronate only Group					
1360	58	F	Scleritis	50	
1360	58	F	Conjunctivitis	68	
2002	58	F	Conjunctivitis	69	
2114	53	M	Iritis	54	
2309	70	F	Iritis	49	
2378	66	F	Eye pain	44	
2602	79	F	Conjunctivitis	4	

7.1.5.6 Additional analyses and explorations

No additional analyses or explorations were performed.

7.1.6 Less Common Adverse Events

See discussions above for the rare, but important adverse events that have been shown to be related to bisphosphonate therapy.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Basic laboratory safety testing was performed in all studies. Special attention was paid to renal laboratories and laboratories of calcium and mineral metabolism. A table of all normal laboratory ranges and pre-defined limits of change can be found in the Appendix 10.2.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Evaluation of laboratory data focused on Protocol 227, which was the only study to evaluated extended treatment.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

As outlined in the table below, there was no clinically significant change in laboratory parameters from beginning to end of study. The change in alkaline phosphatase can be attributed to the action of alendronate on bone.

Study P227: Laboratory Mean Change from Baseline to Week 15 (APT)

	Aln+VitD			Aln		
N, safety population	**360**			**357**		
	Base	**Wk 15**	**%chng**	**Base**	**Wk 15**	**%chng**
Sodium (meq/L)	142.15	142.20	-0.01	142.31	141.90	-0.40
Potassium (meq/L)	4.38	4.38	-0.00	4.42	4.38	-0.02
Creatinine (mg/dL)	0.90	0.91	0.01	0.91	0.91	0.01
AST, SGOT (IU/L)	15.76	15.10	-0.59	15.47	15.59	0.10
ALT, SGPT (IU/L)	13.08	12.31	-0.79	12.71	13.10	0.35
Alkaline Phosphatase (IU/L)	57.02	47.10	-9.43	57.03	48.65	-7.95
WBC ($10^3/\mu L$)	5.69	5.79	0.14	5.73	5.81	0.05
Hematocrit (%)	39.77	39.85	0.16	39.84	40.04	0.26
Hemoglobin (gm/dL)	13.48	13.46	0.00	13.49	13.50	0.03
Platelets ($10^3/\mu L$)	240.24	241.26	1.14	247.76	246.19	0.15

AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

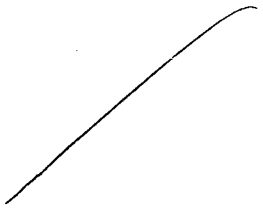
Overall, 81 subjects [61(16.9%) subjects in the alendronate/D_3 group and 20 (5.6%) subjects in the alendronate only group] had laboratory abnormalities reported as adverse events. As outlined in the table below, the most common abnormality was decreased 25 hydroxyvitamin D levels. Decreased 25 hydroxyvitamin D levels occurred in 46 subjects in the alendronate only group and 4 subjects in the alendronate/vitamin D group, and accounts for the imbalance of events between the two treatment arms. Aside from abnormalities in 25 hydroxyvitamin D levels, urine dipstick positive for white blood cells was the most common abnormality and occurred in 2.0% of subjects in the alendronate/vitamin D_3 group and 2.5% of subjects in the alendronate only group.

Study P227: Laboratory Adverse Events			
	Aln+VitD	**Aln**	**Total**
N, safety population	**360**	**357**	**717**
Total subjects with AEs	**17**	**61**	
25-OH vitamin D, decreased	4	46	50
Blood calcium, decreased	2	0	2
Urine calcium, decreased	0	1	1
Urine calcium, increased	2	2	4
Potassium, increased	0	1	1
Glucose, increased	0	2	2
SGOT and/or SGPT increased	1	2	3
Alkaline phosphatase, increased	1	0	1
Cholesterol, increased	0	1	1
Ferritin, decreased	0	1	1
Homocysteine, increased	0	1	1
WBC, decreased	0	2	2
Platelets, decreased	2	1	3
Urinalysis, abnormal	5	7	12

Eight (2.3%) subjects discontinued from study drug therapy due to laboratory events, none were considered serious. All events were due to decreased 25 hydroxyvitamin D levels and all were in the alendronate only group. A total of 8 subjects withdrew prematurely from the study due to decreased 25 hydroxyvitamin D levels, all in the alendronate only arm of the study. As outlined in the table below, most of these discontinued subjects had 25 hydroxyvitamin D levels below 15 ng/mL at study onset.

Study P227: Withdrawals due to Low Vitamin D Levels								
Patient	Age	Sex	W/D day	Vitamin D Level (ng/mL)				Comment
				baseline[1]	Wk 5	Wk 10	Wk 15	
1009	54	F	34	10				
1097	69	F	41	9				
1161	82	F	43	13				
1274	48	F	106	9				
1309	73	F	71	10				
2113	64	F	71	14				
2201	73	F	78	16				
2233	69	F	43	16				

[1] average of the 2 pre-randomization values



The table below outlines the marked laboratory abnormalities. There were no clinically significant differences between treatment groups with the exception of 25 hydroxyvitamin D levels.

Protocol 227: Laboratory Abnormalities Outside Predefined Limits of Change			
	Aln+VitD	Aln	Difference %
N, safety population	**360**	**357**	**(95% CI)**
25-OH Vitamin D level			
Value < 9	4 (1.1)	46 (13.1)	-12.0 (-16.0,-8.4)
Serum Calcium (mg/dL)			
Value < 8	1 (0.3)	2 (0.6)	-0.3 (-1.8,1.1)
Value < 8.5	10 (2.8)	9 (2.6)	0.2 (-2.3,2.8)
Value > 10.5	5 (1.4)	2 (0.6)	0.8 (-0.9,2.7)
Urine Calcium (mg/24hr)			
Increase ≥ 25%	62 (18.1)	55 (16.5)	1.6 (-4.1,7.3)
Value > 300mg/24hr	40 (11.7)	28 (8.4)	3.3 (-1.3,7.9)
Value < 50mg/24hr	22 (6.4)	29 (8.7)	-2.3 (-6.4,1.8)
Serum Phosphate (mg/dL)			
Value < 2.0	2	2 (0.6)	-0.6 (-2.1,0.6)
Decrease ≥ 30% and value < LLN (2.50)	4 (1.1)	7 (2.0)	-0.9 (-3.1,1.1)
Increase ≥ 30% and value > ULN (4.50)	2 (0.6)	2 (0.6)	-0.0 (-1.6,1.5)
Sodium (meq/L)			
Decrease ≥ 10 and value < LLN (133)	1 (0.3)	0	0.3 (-0.8,1.6)
Increase ≥ 10 and value > ULN (145)	1 (0.3)	0	0.3 (-0.8,1.6)
Potassium (meq/L)			
Increase ≥ 0.5 and value > ULN (5.00)	12 (3.5)	11 (3.3)	0.2 (-2.7,3.1)
Blood Urea Nitrogen (			
Increase ≥ 50%	17 (4.8)	11 (3.2)	1.6 (-1.4,4.8)
Increase ≥ 50% and baseline >ULN	0	1 (0.3)	-0.3 (-1.6,0.8)
AST, SGOT (IU/L)			
Increase ≥ 50% and value > ULN (25.00)	4 (1.1)	5 (1.5)	-0.4 (-2.3,1.6)
ALT, SGPT (IU/L)			
Increase ≥ 50% and value > ULN (25.00)	2 (0.6)	4 (1.2)	-0.6 (-2.4,1.1)
Alkaline Phosphatase (IU/L)			
Increase ≥ 50% and value > ULN (90.00)	2 (0.6)	2 (0.6)	-0.0 (-1.6,1.5)
WBC (10^3/μL)			
Decrease ≤ 20% and value < LLN (4.80)	14 (4.1)	6 (1.8)	2.3 (-0.3,5.1)
Value < LLN (4.80)	75 (21.6)	84 (24.6)	-3.0 (-9.3,3.3)
Increase ≥ 20% and value > ULN (10.80)	3 (0.9)	1 (0.3)	0.6 (-0.9,2.2)
Hematocrit (%)			
Decrease ≤ 20% and value < LLN (42)	0	1 (0.3)	-0.3 (-1.6,0.8)
Hemoglobin (gm/dL)			
Decrease ≤ 20% and value < LLN (14.0)	0	1 (0.3)	-0.3 (-1.6,0.8)
Platelets (10^3/μL)			
Decrease ≤ 25% and value < LLN (150)	1 (0.3)	2 (0.6)	-0.3 (-1.8,1.1)

7.1.7.4 Additional analyses and explorations

No additional analyses or explorations were performed.

7.1.7.5 Special assessments

Hypercalcemia and Hypercalciuria: Hypercalcemia and hypercalciuria are important side effects of over-replacement with vitamin D. Nine subjects (2 in the alendronate only group and 7 in the alendronate/vitamin D_3 group) had at least one calcium level that met criteria for hypercalcemia (> 10.5 mg/dL). There was no consistent pattern in the elevations seen. The highest calcium level in any subject was 10.9 mg/dL.

Protocol 227: Serum Calcium Levels of Subjects with Hypercalcemia

			Serum calcium level (mg/dL)				
AN	Age	Sex	Visit 1 Screen	Visit 3 Baseline	Visit 5 Day 35	Visit 6 Day 71	Visit 7 Final
Alendronate Only Group							
2098	54	F	10.3	10.3			
2511	70	F	10.0	10.2			
Alendronate + D Group							
1025	74	F	9.3	9.9			
2136	60	F	10.8	10.5		d/c'd, pt moved	
2232	76	F	10.7	10.2			
2287	66	F	9.5	9.6			
2354	63	F	10.6	10.7		d/c'd, AE – hot flush	
2359	66	F	10.1	9.7			
2551	54	F	10.6	10.5			

Overall, 18.1% of subjects in the alendronate/vitamin D_3 group had an increase in urine calcium greater than 25% over baseline compared to 16.5% of the alendronate only group, as outlined in the table below. As well, 11.7% of subjects in the alendronate/vitamin D_3 group had urine calcium greater than 300mg/day, compared to 8.4% in the alendronate only group. The percentage of subjects with a urine calcium that was both >300 mg/day and increased >25% over baseline was similar in both treatment groups. The occurrence of hypercalciuria did not change when analysis was performed based on daily calcium intake.

Study P227: Proportion of Patients with Hypercalciuria (APT)

	Aln+VitD	**Aln**
N	**360**	**357**
Increase ≥ 25%	62 (18.1)	55 (16.5)
Level > 300mg/day	40 (11.7)	28 (8.4)
Increase ≥ 25% + Level > 300mg/day	14 (4.1)	14 (4.2)
Calcium Intake 34-805 mg/day	170	161
	7 (4.1)	7 (4.3)
Calcium Intake 805-2126 mg/day	163	167
	7 (4.3)	7 (4.2)

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In Protocol 227, vital signs, including heart rate, blood pressure and weight were evaluated at baseline and Weeks 5, 10, and 15.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Evaluation of vital sign data focused on Protocol 227, which was the only study to evaluate extended treatment.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

As outline in the table below, there were no clinically significant changes in vital signs (systolic and diastolic blood pressure, heart rate, or body weight) during the study.

Study P227: Vital Signs Mean Change from Baseline to Week 15 (APT)						
	Aln+VitD			**Aln**		
N, safety population	**360**			**357**		
	Base	**Wk 15**	**chng**	**Base**	**Wk 15**	**chng**
Systolic blood pressure (mmHg)	131.30	130.02	1.01	132.62	131.26	-1.34
Diastolic blood pressure (mmHg)	77.52	76.37	-1.01	77.68	76.94	-0.69
Heart rate (bpm)	70.23	70.85	1.10	69.30	70.90	1.72
Weight (kg)	62.95	63.50	0.62	64.60	64.95	0.61

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

As outlined in the table below, a total of 17 subjects reported adverse events related to vital signs. None were serious adverse events. The events were evenly distributed between the groups.

Study P227: Clinical Adverse Events			
	Aln+VitD	**Aln**	**Total**
N, safety population	**360**	**357**	**717**
Blood pressure, increased	2	2	4
Heart rate irregular	1	1	2
Cardiac murmur	3	1	4
Intraocular pressure increased	0	1	1
Weight increased	1	4	5
Weight decreased	1	0	1

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations were performed.

7.1.9 Electrocardiograms (ECGs)

No ECG analyses were performed in the submitted studies.

7.1.10 Immunogenicity

No immunogenicity data have been submitted in this NDA. Alendronate is a non-peptide that would not be expected to elicit an immune response.

7.1.11 Human Carcinogenicity

Data from preclinical studies do not suggest that alendronate is genotoxic or oncogenic. Long-term studies in animals have not been performed to evaluate the carcinogenic potential of vitamin D_3 (cholecalciferol). Evaluation of 1,25 $(OH)_2$ vitamin D_3 (calcitriol), the biologically active form of cholecalciferol is not mutagenic in vitro in the Ames test, nor is it genotoxic in vivo in the mouse micronucleus test.

7.1.12 Special Safety Studies

No special safety studies have been performed.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no withdrawal phenomena or abuse potential with bisphosphonates such as alendronate.

7.1.14 Human Reproduction and Pregnancy Data

Animal reproduction studies have not been conducted with vitamin D_3. There are no adequate and well controlled studies in pregnant women. This combination drug is indicated for treatment of postmenopausal osteoporosis. Concern regarding the use of bisphosphonates in women of childbearing age and the potential for fetal toxicity after remote exposure to the drug has led to class labeling precautions.

7.1.15 Assessment of Effect on Growth

Alendronate has been studied in a high risk population of children with the metabolic bone disease osteogenesis imperfecta. Because of the altered growth pattern of children with this disease, it is not possible to adequately assess alendronate's effect on growth.

7.1.16 Overdose Experience

A total of 3 subjects had an overdose of study drug in Protocol 227. One subject in the alendronate only group took 5 study tablets in a period of time when she should have taken 4; one subject in the alendronate/vitamin D_3 group took study therapy 4 days in a row and then 2 days in a row for a total of 6 doses in seven days; and one subject in the alendronate/vitamin D_3 group took 2 tablets from the same bottle on the same day. None of the patients experienced an adverse event.

7.1.17 Postmarketing Experience

Alendronate is currently marketed worldwide in over 90 countries for the treatment of osteoporosis. The side effect profile of alendronate is well described. The alendronate/vitamin D_3 combination tablet is not approved in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Protocol 227 was a 15-week, randomized, double-blind, multicenter, active-controlled study which enrolled men and postmenopausal women with osteoporosis. A total of 717 subjects were enrolled in the trial, 95% of which completed the study. Protocol 226 was an open-label, randomized, 2-part, 2-period, crossover study in 244 healthy non-pregnant women and men age 18 to 65. Ninety-six percent of enrolled subjects completed the study.

7.2.1.2 Demographics

In Protocol 227, the study population was predominantly women (95.1%) with only 4.9% men. As well, the entire population was predominantly Caucasian (98.6%). The mean age was 66.8 years (range 35-89). Baseline lumbar spine BMD T-score was -3.02. Approximately 22% of patients had 25 hydroxyvitamin D levels below 15, indicating vitamin D insufficiency. In Protocol 226, the average age of the study population was 40.8 years. Fifty five percent were women and 45% were men. The majority (74%) of subjects enrolled in Part I of the study were Hispanic. In Part II of the study, 100% of subjects were Caucasian.

7.2.1.3 Extent of exposure (dose/duration)

In Protocol 227, subjects received 70mg alendronate or 70mg alendronate/2800IU vitamin D_3 weekly. The mean number of weeks on study drug was 14.7 for the alendronate only group and 14.8 for the alendronate/vitamin D_3 group.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Protocols 183 and 220 were reviewed, but offered no additional safety information.

7.2.2.2 Postmarketing experience

The alendronate/vitamin D_3 combination tablet is not approved in any country.

7.2.2.3 Literature

A review of the literature was conducted to assess the safety of intermittent dosing for vitamin D supplementation and levels at which vitamin D toxicity occurs. Current recommendations of the IOM sets the upper limit of intake for vitamin D as 2000IU daily. Several studies have challenged this upper limit and evaluated vitamin D dosing at 1000IU or 4000IU daily and 100,000IU every 4 months[17,18]. These regimens were found to be safe. However, there remains significant controversy regarding what dose of vitamin D is sufficient versus at what dose is replacement excessive[19].

7.2.3 Adequacy of Overall Clinical Experience

Alendronate has been adequately assessed in the company's extensive development program.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Adequate pre-clinical testing has been done and previously reviewed for alendronate. While studies in animals have been performed with other vitamin D agents, there is little testing specific to cholecalciferol (vitamin D_3).

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing performed was adequate and focused on the known clinical effects of both alendronate and vitamin D.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Adequate in-vitro testing has been performed in previously reviewed alendronate submissions.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The adverse event profile of both alendronate and vitamin D are well known and documented.

7.2.8 Assessment of Quality and Completeness of Data

The data submitted and reviewed for safety were complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

Protocol 227 was submitted in the safety update, and provides the basis for the main safety review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The studies submitted with this NDA indicate that combination alendronate/vitamin D_3 weekly tablet is safe. There were no unexpected safety findings uncovered during the review. There was an imbalance between the alendronate only group and the alendronate/vitamin D_3 group in the number of subjects who withdrew due to laboratory adverse events. All of the withdrawals occurred in the alendronate group and were due to low 25 hydroxyvitamin D levels. This was not unanticipated, due to the lack of vitamin D supplementation in the alendronate only group and acts to stress the importance of adequate vitamin D nutrition.

The upper limit of normal intake for vitamin D is considered 2000 IU/day. While the vitamin D_3 dosing with the combination alendronate/vitamin D_3 weekly tablet exceeds this amount on the day of dosing, there was no evidence of persistent hypercalcemia or hypercalciuria in study subjects.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The current dosing guidelines for the alendronate 70mg once weekly tablet were followed in Protocol 227 and should be maintained at the present recommendations. In addition, it is recommended that adequate calcium and vitamin D to ensure nutritional sufficiency be included as part of the regimen for any patient on alendronate therapy.

8.2 Drug-Drug Interactions

There does not appear to be any untoward interaction between alendronate and cholecalciferol such that the bioavailability of alendronate of vitamin D_3 is altered.

8.3 Special Populations

Alendronate 70mg once weekly daily is currently approved for therapy in postmenopausal women and men with osteoporosis. In the 10-year experience with the drug, there is no indication of altered safety effects due to race, gender or age.

8.4 Pediatrics

The proposed indication in this NDA is restricted to postmenopausal women and men with osteoporosis. The efficacy and safety of alendronate are currently being evaluated in a high risk pediatric population.

9 OVERALL ASSESSMENT

9.1 Conclusions

The bioavailability and effectiveness of the alendronate 70mg once weekly tablet is not altered by the addition of 2800IU vitamin D_3. The addition of vitamin D_3 may confer a protective effect against the expected decrease in serum calcium and subsequent increase in PTH level seen with alendronate therapy.

It has been decided that the sponsor must comply with 21 CFR 300.50 for the combination of 2 or more drug products. In this case, the alendronate/vitamin D_3 combination tablet should be evaluated on the basis of the current Fosamax indication - treatment of osteoporosis in postmenopausal women and treatment to increase bone mass in men with osteoporosis. The data submitted in Protocol 227 indicate that there is no compromise of alendronate's effect on bone, as evidenced by the biomarker data.

In their argument regarding the need for comply with 21 CFR 300.50, the sponsor contends that vitamin D does not make a contribution to the treatment of osteoporosis. They state that vitamin D is known to treat osteomalacia as the implied over the counter claim. While it is true that the index disease for vitamin D deficiency is osteomalacia (rickets in children), there is clear evidence that vitamin D deficiency and insufficiency are associated with osteoporosis and fracture. As outlined by Heaney, vitamin D insufficiency results in several levels of physiologic and biochemical change, all of which are associated with bone pathology [20]. The first 2 stages involved, calcium malabsorption and elevation of PTH levels, result in osteoporosis. Only if the vitamin D deficiency is severe and prolonged, will osteomalacia develop. In most cases, vitamin D deficiency and insufficiency present solely as osteoporosis. Therefore, vitamin D supplementation does have a role in the treatment of osteoporosis. In addition, calcium and vitamin D supplementation are the base therapies in the osteoporosis treatment algorithm proposed in the 2004 Surgeon General's report on bone health and osteoporosis[21].

Therefore, it is necessary for the sponsor to provide a discussion and evidence to support vitamin D_3's efficacy in the treatment of osteoporosis. Studies in the literature specifically evaluating vitamin D supplementation in preventing fractures have been mixed. A meta-analysis conducted in 2002 reviewed the effect of vitamin D on bone density and fractures in postmenopausal women[22]. They concluded that Vitamin D reduced the incidence of vertebral fractures (relative risk 0.63, 95% CI 0.45– 0.88, $P < 0.01$) and showed a trend toward reduced incidence of nonvertebral fractures (RR 0.77, 95% CI 0.57–1.04, $P = 0.09$). Most patients in the trials that evaluated vertebral fractures received hydroxylated vitamin D, and most patients in the trials that evaluated nonvertebral fractures received standard vitamin D. Assessment of BMD changes revealed that hydroxylated vitamin D had a consistently larger impact on bone density than did standard vitamin D. One confounding factor to this meta-analysis is that studies were included irrespective of whether calcium was added to vitamin D in the treatment group as calcium itself increases BMD.

With regard to the appropriateness of the vitamin D dose in the combination tablet, this reviewer has great concern that the dose of vitamin D_3 utilized in Protocol 227 is not sufficient to meet demands and provide adequate vitamin D status. While the proportion of subjects with insufficient serum 25-hydroxyvitamin D levels (when defined as <15 ng/mL) was significantly lower in the combination alendronate/vitamin D_3 group when compared to the alendronate alone group, a significant number of subjects remained at 25 hydroxyvitamin D levels that many experts would consider insufficient. Overall, after 15 weeks of therapy, 61% of subjects in the alendronate/vitamin D_3 combination tablet group had 25 hydroxyvitamin D levels that did not exceed 25ng/mL (compared to 78% in the alendronate only group) while 78% of subjects in the alendronate/vitamin D_3 combination tablet group had 25 hydroxyvitamin D levels less than 30ng/mL (compared to 85% in the alendronate only group). Clearly, results of this study show that use of the combination tablet with 2800IU vitamin D_3 weekly did not achieve or even maintain optimal 25 hydroxyvitamin D levels in some subjects. The current adequate intake of vitamin D set by the Institute of Medicine is 400IU per day for adults age 51-70 years and 600IU per day in adults over age 70 years[23]. Patients over age 70 years are at high risk of fracture, they are a population that will be targeted for anti-resorptive therapy. Supplementation with the currently proposed dose of 70mg alendronate/2800IU vitamin D_3 may be insufficient to achieve or even maintain optimal 25 hydroxyvitamin D levels in this population. Therefore, higher doses of vitamin D_3 should be investigated.

9.2 Recommendation on Regulatory Action

This reviewer believes that the alendronate once weekly combination tablet of 70mg alendronate and 2800IU vitamin D_3 is approvable, contingent upon the fulfillment of the following deficiencies:

- The sponsor should provide evidence of Vitamin D's role in osteoporosis treatment and fracture prevention in postmenopausal women and men.
- The sponsor should discuss and provide support for the benefit of combination alendronate/vitamin D_3 therapy compared with alendronate therapy for treatment of osteoporosis.
- The sponsor should provide an explanation for the suboptimal increases in 25 hydroxyvitamin D levels achieved with the combination alendronate/vitamin D_3 tablet when compared with levels achieved with other vitamin D_3 supplements, as detailed in Table 2.5:1 in the clinical overview section of the NDA submission.
- The sponsor should propose a development plan for combination tablet(s) with doses of vitamin D_3 that provides an adequate dose range which will allow satisfactory 25 hydroxyvitamin D levels to be achieved. The bioequivalence and bioavailability of alendronate will need to be confirmed with any higher vitamin D_3 doses.
- The sponsor should provide the financial disclosure information for Protocol 227.

9.5 Comments to Applicant

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study P227: A 15-week, double-blind, randomized, active-controlled, multicenter study with 24-week extension to evaluate the safety, tolerability, and efficacy of Alendronate 70mg plus Vitamin D_3 2800IU combination tablet in men and postmenopausal women with osteoporosis

Objectives: The objectives of this study were:

Primary

1. To evaluate the efficacy of alendronate 70mg/vitamin D_3 2800IU administered once weekly as a combination tablet to reduce the proportion of patients with vitamin D insufficiency (serum 25-hydroxyvitamin D <15 ng/mL) in men and postmenopausal women with osteoporosis, compared to alendronate 70mg alone after 15 weeks of treatment.

Secondary

1. To evaluate the efficacy of alendronate 70mg/vitamin D_3 2800IU administered once weekly as a combination tablet to reduce the risk of vitamin D deficiency (serum 25-hydroxyvitamin D <9 ng/mL) in men and postmenopausal women with osteoporosis, compared to alendronate 70mg alone after 15 weeks of treatment.
2. To evaluate the mean serum 25-hydroxyvitamin D level after treatment with alendronate 70mg/vitamin D_3 2800IU administered once weekly as a combination tablet compared to alendronate 70mg alone after 15 weeks of treatment.
3. To assess the effect of alendronate 70mg/vitamin D_3 2800IU administered once weekly as a combination tablet for 15 weeks on the rate of bone turnover as assessed by biochemical markers (BSAP, NTx), serum calcium, 24-hour urine calcium, serum phosphate, and serum parathyroid hormone compared to alendronate 70mg alone.
4. To evaluate the safety and tolerability of alendronate 70mg/vitamin D_3 2800IU administered once weekly as a combination tablet in men and postmenopausal women with osteoporosis.
5. To estimate the proportion of patients with a serum 25-hydroxyvitamin D ≥15 ng/mL after 15 weeks of treatment with the alendronate 70mg/vitamin D_3 2800 IU combination tablet.

Study Design: This was a 15-week, randomized, double-blind, multicenter, active-controlled study to assess the safety, tolerability, and efficacy of alendronate/vitamin D_3 tablets in men and postmenopausal women with osteoporosis. The alendronate/vitamin D_3 tablet was evaluated against the alendronate once weekly marketed tablet. The primary efficacy endpoint was the

ability of the alendronate/vitamin D_3 tablet to reduce the proportion of patients with vitamin D insufficiency (serum 25-hydroxyvitamin D <15 ng/mL) compared to alendronate alone after 15 weeks of treatment.

Population: The intended study population was men and women, aged 40 to 90 years of age. Subjects were enrolled at 54 four clinical centers in 11 countries (France, Germany, Hungary, Italy, Netherlands, Russian Federation, Spain, Sweden, Switzerland, United Kingdom, and the United States).

Inclusion Criteria

- Male or postmenopausal female (as diagnosed by a history of the absence of menstrual periods during the 6 months preceding randomization [with appropriate endocrine confirmation in non-ovariectomized women, younger than 55 and not 18 months since last menses]), aged 40 to 90 years.
- The patient was willing to limit direct sunlight exposure during the course of the 15-week study (e.g., avoid sunbathing, tanning salons) and applied sunscreen (SPF 15 or greater) to exposed skin if exposure to direct sunlight exceeded 1 hour.
- The patient was in satisfactory health, based on medical history, physical examination, and laboratory screening evaluation.
- The patient had spine or hip anatomy suitable for dual-energy x-ray absorptiometry.
- The patient had lumbar spine BMD in g/cm2 (— [L1 to L4] <0.772· — [L1 to L4] <0.880) or femoral neck BMD — <0.572; — <0.680) which corresponds to a BMD T-score at or below –2.5 SD, that was >2.5 below the mean for normal premenopausal women.
- The patient voluntarily agreed to participate in the study, understood the procedures, and risks involved with this study, and signed a written informed consent form.

Exclusion Criteria

- The patient was, in the opinion of the investigator, mentally or legally incapacitated such that informed consent could not be obtained.
- The patient had significant unexplained abnormalities other than those listed as exclusion criteria, as judged by the investigator, on prestudy clinical examination or on the laboratory measurements that were carried out prior to randomization into the study.
- The patient was contraindicated to bisphosphonate therapy:
    - The patient had abnormalities of the esophagus which delay esophageal emptying, such as stricture or achalasia.
    - The patient had an inability to stand or sit upright for at least 30 minutes.
    - The patient had hypersensitivity to any component of the product.
    - The patient had uncorrected hypocalcemia.
- The patient had one or more of the following concomitant conditions:
    - Significant end-organ disease, i.e., genitourinary, cardiovascular, hepatic, renal, endocrine, hematologic, psychiatric, or pulmonary disease, which, in the opinion of the investigator, posed an added risk to the patient or would impair the patient's ability to complete the trial or confound the results.
    - Myocardial infarction within 6 months of screening visit.
    - History of or evidence for impaired renal function defined as a serum creatinine value ≥2.0 mg/dL.
    - Malabsorption syndrome.
    - Active thyroid disease, as demonstrated by an abnormal serum TSH (measured with an ultra-sensitive assay) and serum thyroxine. If received thyroid hormone replacement, the dose must not have been changed in the prior 3 months.

  - Uncontrolled hypertension (e.g., blood pressure [mm Hg] >180 systolic or >105 diastolic).
- Concomitant disease of bone or mineral metabolism, including:
  - History of, or evidence for metabolic bone disease (e.g., Paget's, osteomalacia).
  - Vitamin D deficiency or any form of osteomalacia. If serum 25-hydroxyvitamin D level <15 ng/mL but greater than or equal to 9 ng/mL, serum PTH and alkaline phosphatase must be normal. If serum 25-hydroxyvitamin D level <9 ng/mL, the patient must be excluded.
  - The patient had a serum calcium less than the lower limit of normal not explained by decreased protein binding or alkaline phosphatase greater than 10% the upper limit of normal
  - The patient had a history of any form of cancer, with the following exceptions:
  - Adequately treated superficial basal or squamous cell carcinoma of the skin or cervical carcinoma in situ
  - Solid tumor definitively treated without any history of recurrence for at least 5 years prior to study entry
  - Breast cancer ≤Stage II and tumor size <3 cm, not locally invasive or have lymph node involvement at the time of surgery
  - Prostate cancer curatively treated by resection and/or radiation, and is not on hormonal therapy
- The patient was, at the time of entry, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last 5 years) of drug or alcohol abuse
- The patient had a spine or hip anatomy, or excessive weight, that was unsuitable for BMD measurement
- The patient had insufficient calcium intake, defined as combined dietary and supplement intake less than 800 mg of elemental calcium daily and was unwilling to further supplement intake during the study
- 1The patient had a calcium intake of greater than 1500 mg of calcium per day (including the study supplement)
- The patient intended to move within the duration of the study, rendering follow-up per protocol, impractical
- The patient was participating or had participated (within 6 weeks) in another study of an investigational drug
- The patient was currently receiving treatment with any of the following agents with effects on bone or calcium metabolism:
  - Oral bisphosphonate (including alendronate, risedronate, etidronate or tiludronate), or intravenous pamidronate
  - Fluoride >1 mg/day
  - Calcitonin (subcutaneous or intranasal).
  - Vitamin A (excluding beta-carotene) in excess of 10,000 units/day.
  - Vitamin D in excess of 800 units/day prior to screening.
  - Anticonvulsants, including barbiturates, hydantoins, and carbamazepine.
  - Glucocorticoids (with the exception of over-the-counter topical preparations and inhaled glucocorticoid for the short term treatment of asthma).
  - Parathyroid hormone.
  - Lithium.
  - Anabolic steroids (including tibolone).
  - Treatment with an immunosuppressant (e.g., cyclosporine, azathioprine, but not methotrexate for the treatment of rheumatoid arthritis) within the previous year.
  - SERMs (Selective Estrogen Receptor Modulators), e.g., raloxifene, tamoxifen.
  - Estrogen replacement therapy (excluding locally-acting estrogen creams)• Testosterone replacement unless the patient has been on a stable dose for at least 6 months.
  - Strontium.

- The patient had received any of the following agents with effects on bone or calcium metabolism:
  - Any previous treatment with a bisphosphonate for more than 2 weeks within the past 6 months, or for more than 1 month within the past year.
  - Estrogen (excluding locally-acting vaginal estrogen creams), estrogen analogues (e.g., raloxifene, tamoxifen), tibolone or other anabolic steroids for >2 weeks within 6 months of study entry.
  - Calcitonin (subcutaneous or intranasal) within 1 month of study entry.
  - Fluoride >1 mg/day for >2 weeks within 3 months of study entry.
- The patient was unwilling to refrain from use of any dietary supplements (including multivitamins) that contained vitamin D2 or D3, including fish or other animal oil extracts that contain substantial amounts of vitamin D for the 15-week base study.
- The patient was unwilling to refrain from the use of vitamin D supplements exceeding 1000 IU/day (in addition to study drug) in the extension study.

COMMENT: The inclusion and exclusion criteria are extensive and appear appropriate. Of note, subjects with gastrointestinal disease were not excluded from enrollment, nor were subjects taking medications affecting the gastrointestinal tract, such as non-steroidal anti-inflammatory drugs.

Study Medication: Subjects were randomized 1:1 to receive either 70mg alendronate/2800IU vitamin D_3 combination tablet or 70mg alendronate. A "double-dummy" treatment design was used. On Day 1, each subject received 1 bottle containing 16 alendronate/vitamin D_3 tablets or 16 placebo tablets (Bottle A), as well as 16 alendronate tablets, or placebo tablets (Bottle B). Subjects were instructed to take 1 tablet from each bottle on a once weekly basis for the full duration of the study. Patients were told to take the tablets (one at a time) upon arising in the morning at least 30 minutes before breakfast with a full glass of water (6 to 8 ounces), followed by at least 4 ounces of additional water after the second tablet was taken. Patients were told to remain fasting (except for plain water) and upright for at least 30 minutes after taking the tablet and until consuming the first food of the day. If a weekly dose was forgotten, patients were told to take it on the day they remember (as long as 2 doses were not taken on the same day) and then return to the scheduled day of the week for all subsequent doses.

Efficacy Measures

Primary Endpoint: Measurement of 25-hydroxyvitamin D was performed at screening, Weeks 5, 10 and 15.

Secondary Efficacy Endpoints: Biochemical markers of bone turnover, urine N- telopeptide of Type 1 collagen corrected for creatinine (NTx) and serum bone-specific alkaline phosphatase (BSAP) were assessed at screening, Weeks 5, 10 and 15. Parathyroid hormone and serum calcium were assayed in samples collected at screening, Day 1, and Weeks 5, 10, and 15. Urine calcium and creatinine was collected at Visits 2 and 7.

Safety Measures: Clinical evaluations were performed at every visit and laboratory measurements (serum chemistry, hematology, urine chemistry, and urinalysis) were performed at screening, Day 1 (randomization), and Weeks 5, 10, and 15. All adverse experiences (clinical and laboratory) were recorded on the adverse experience case report forms throughout the study.

Study Methods:

Bone Mineral Density: Bone Mineral Density was measured using DXA (dual energy x-ray absorptiometry), on either an — or — densitometer. Measurements of the spine, and/or femoral neck were performed. The baseline BMD measurement was completed before randomization occurred. All scans were analyzed by the local technician to determine patient eligibility. Each investigational site performed the scans according to their own clinical practice.

Sunlight Exposure: Sunlight exposure was limited during the study. Patients were instructed to avoid sunbathing, tanning salons, and exposure to direct sunlight for more than 1 hour without sunscreen [SPF 15 or greater].

Withdrawal criteria: Subjects had the right to withdraw from the study at any time or could be dropped from the study at the discretion of the investigator, should any untoward effects occur.

During the study if a patient's 25-hydroxyvitamin D level fell below 9 ng/mL, the patient was taken off of study therapy and given a rescue dose of vitamin D (800 to 1000 IU per day) by the investigator. The patients remained in the study off of study drug, and were re-evaluated at subsequent clinic visits. If the vitamin D deficiency was not corrected by the final visit (Visit 7), additional unscheduled visits were provided at appropriate intervals (2 to 4 weeks) to document that the 25-hydroxyvitamin D increased into the normal range.

Statistical Analyses

Hypothesis

Primary

In men and postmenopausal women with osteoporosis, oral alendronate 70mg/vitamin D_3 2800IU administered once weekly as a combination tablet will reduce the proportion of patients with serum 25-hydroxyvitamin D levels <15 ng/mL, compared to patients administered alendronate 70mg tablets alone after 15 weeks of treatment. The serum 25-hydroxyvitamin D level of 15 ng/mL is defined as the level below which vitamin D insufficiency begins.

Secondary

1. In men and postmenopausal women with osteoporosis, oral alendronate 70mg/ vitamin D_3 2800IU administered once weekly as a combination tablet will reduce the proportion of patients with serum 25-hydroxyvitamin D levels <9 ng/mL, compared to patients administered alendronate 70mg tablets alone after 15 weeks of treatment. The serum 25-hydroxyvitamin D level of 9 ng/mL is defined as the level below which vitamin D deficiency begins.
2. Treatment with alendronate 70mg/vitamin D_3 2800IU administered once weekly as a combination tablet for 15 weeks will be sufficiently safe and well tolerated to permit its use in patients with conditions for which alendronate 70mg is indicated.

Sample Size: For the primary hypothesis, a sample size of n=340 evaluable patients per treatment group, after 15 weeks of treatment with alendronate/vitamin D_3, would have 90% power to detect a difference of at least 11.3% in the combination group(alpha=0.05, two-tailed). This calculation assumed that after 15 weeks of treatment, the 25-hydroxyvitamin D insufficiency (<15 ng/mL) rate would be 35% in the alendronate only group.

Analysis Populations: The approach for the primary analysis was the all patients treated (APT) population that included all randomized patients who took at least one dose of study drug and had at least one post randomization measurement. Patients who dropped out of the study for any reason were included in the analysis of the APT population as long as they had at least one post baseline efficacy measurement. The primary analysis imputed missing data by carrying the previous post randomization measurement forward. Other analysis populations included the Extended All Patients treated (EAPT) population and the Per Protocol (PP) population. The EAPT approach included data collected after discontinuation of blinded study therapy in addition to data collected on blinded study therapy. This approach also imputed missing data by carrying the previous post randomization measurement forward. The PP population excluded those patients who were identified as protocol violators and/or who discontinued the study therapy due to low 25-hydroxyvitamin D levels from the time point they missed cumulatively 4 study doses. The analysis of the PP population was considered the primary analysis for the bone biochemical markers NTx and BSAP.

Protocol Amendments: The protocol was amended once during the course of the study (November 10, 2003). The amendment included administrative changes the addition of a Falls Questionnaire, the definition of study therapy overdose, as well as the addition of a secondary objective. The secondary objective was added as the result of Agency feedback.

- The objective reads: "To estimate the proportion of patients with a serum 25-hydroxyvitamin D ≥15 ng/mL after 15 weeks of treatment with the alendronate 70-mg/vitamin D_3 2800 IU combination tablet."
- A change to the planned analyses was made so that patient allocation number (AN) 1273 and patient AN 1300 had their mean baseline serum 25- hydroxyvitamin D results rounded up to the next integer.
- Upon unblinding of the primary endpoint laboratory values, it was noted that nine 25-hydroxyvitamin D results were reported as undetectable. In approximately half of the patients these results were inconsistent with prior or subsequent measurements. Therefore, all nine samples with undetectable levels were reanalyzed.

Results

Patient Disposition: A total of 1132 subjects were screened and 82 (7.2%) were excluded from the study due to serum 25-hydroxyvitamin D levels <9 ng/mL. A total of 717 subjects were enrolled into the study. As outlined in the table below, 95% of subjects completed the 15 week

study with 92% continuing into the 24 week extension study. Clinical adverse events was the most common reason for discontinuation, occurring in 6% of enrolled subjects.

Study P227: Disposition			
	Aln+VitD	**Aln**	**Total**
N	360 (%)	357 (%)	717 (%)
Completed	**338 (93.9)**	**335 (93.8)**	**673 (93.8)**
Completed/Continuing	332 (92.2)	326 (91.3)	658 (91.7)
Completed/Not Continuing	6 (1.7)	9 (2.5)	15 (2.1)
Adverse Event, Clinical	4 (1.1)	1 (0.3)	5 (0.7)
Adverse Event, Lab	0	8 (2.2)	8 (1.1)
Other	1 (0.3)	0	1 (0.1)
Protocol Violation	1 (0.3)	0	1 (0.1)
Withdrawals	**22 (6.1)**	**22 (6.2)**	**44 (6.1)**
Adverse Event, Clinical	14 (3.9)	16 (4.5)	30 (4.1)
Patient Moved	1 (0.3)	1 (0.3)	2 (0.3)
Withdrew Consent	2 (0.6)	2 (0.6)	4 (0.6)
Other	1 (0.3)	1 (0.3)	2 (0.3)
Protocol Violation	4 (1.1)	2 (0.6)	6 (0.8)
APT Analysis Population	**357 (99.2)**	**351 (98.3)**	**708 (98.7)**
PP Analysis Population	**324 (90.0)**	**291 (81.5)**	**615 (85.8)**

Protocol Violations: As outlined in the table below, there were a total of 31 subjects (15 in the alendronate/vitamin D_3 group and 16 in the alendronate alone group) with protocol violations in the study. The most common violations was use of concomitant medications (mainly, vitamin D supplements).

Study P227: Protocol Violations			
	Aln+VitD	**Aln**	**Total**
N	360 (%)	357 (%)	717 (%)
Total	**15**	**16**	**31**
D/C due to low Vit D level	1 (0.3)	7 (2.0)	8 (1.1)
Concomitant therapy, total	8 (2.2)	4 (1.1)	12 (1.7)
Vitamin D	4 (1.1)	2 (0.6)	6 (0.8)
Other	4 (1.1)	2 (0.6)	6 (0.8)
Study drug noncompliance	3 (0.8)	4 (1.1)	7 (1.0)
Baseline lab value	3 (0.8)	1 (0.3)	4 (0.6)

Two subjects were prematurely unblinded due to serious adverse events. Both were randomized to alendronate once-weekly. One subject, a 68 year old woman with chronic gastritis experienced dry heaves and abdominal pain at Visit 4. The patient was unblinded by the Sponsor's internal safety surveillance group. The second subject, an 85 year old woman with multiple medical problems including renal insufficiency and intermittent anemia developed worsening anemia at Visit 4.

Demographics: The demographics of the study population are outlined in the table below. The population was predominantly women (95.1%) with only 4.9% men. As well, the entire population was predominantly Caucasian (98.6%). The mean age was 66.8 years (range 35-89). Baseline lumbar spine BMD T-score was -3.02. Approximately 22% of patients had vitamin D levels below 15, indicating vitamin D insufficiency.

Study P227: Demographics			
	Aln+VitD	**Aln**	**Total**
N	360 (%)	357 (%)	717 (%)
Age (yrs.)	66.6 ± 8.7	67.0 ± 8.7	66.8 ± 8.7
< 65 yrs	140 (38.9)	135 (37.8)	275 (38.4)
≥ 65 to < 75 yrs	156 (43.3)	152 (42.6)	308 (43.0)
≥ 75 yrs	64 (17.8)	70 (19.6)	134 (18.7)
Gender			
Female	350 (97.2)	332 (93.0)	682 (95.1)
Male	10 (2.8)	25 (7.0)	35 (4.9)
Race			
Caucasian	354 (98.3)	353 (98.9)	707 (98.6)
Black	4 (1.1)	1 (0.3)	5 (0.7)
Oriental	0	0	0
Hispanic	2 (0.6)	2 (0.6)	4 (0.6)
Other	0	1 (0.3)	1 (0.1)
Weight (kg)	62.9 ± 10.7	64.6 ± 11.7	63.8 ± 11.3
Height (cm)	158.5 ± 7.0	159.9 ± 7.2	159.2 ± 7.1
Baseline LS Spine T-score	-3.28	-2.75	-3.02
Baseline 25PH Vit D level	22.4 ± 9.0	22.3 ± 9.4	22.4 ± 9.2
< 15 ng/mL	77 (21.4)	77 (21.6)	154 (21.5)
≥ 15 ng/mL	283 (78.6)	280 (78.4)	563 (78.5)

Concomitant Medications: Of the 717 subjects randomized, approximately 191 (26.6%) reported using at least one prior vitamin D supplement within 14 days of screening. A total of 696 (97.1%) subjects [352 (97.8%) in the alendronate/vitamin D_3 group and 344 (96.4%) in the alendronate alone group] took at least one concomitant medication during the study period.

Study P227: Concomitant Medications			
	Aln+VitD	**Aln**	**Total**
N	360 (%)	357 (%)	717 (%)
Total subjects with at least 1 med	352 (97.8)	344 (96.4)	696 (97.1)
Calcium	313 (86.9)	310 (86.8)	623 (86.9)
Vitamin D supplements	6 (1.7)	9 (2.5)	15 (2.1)
Vitamin / Mineral Supplements	77 (21.4)	73 (20.4)	150 (20.9)
Anti-Acid Medications	41 (11.4)	51 (14.3)	92 (12.8)
Corticosteroids	22 (6.1)	23 (6.4)	45 (6.3)
Estrogens	21 (5.8)	15 (4.2)	36 (5.0)
Anticonvulsants	5 (1.4)	2 (0.6)	7 (1.0)
Anti-inflammatory Medications	75 (20.8)	82 (23.0)	157 (21.9)

Efficacy

Proportion of Subjects with Vitamin D Insufficiency: The primary analyses are based on the all-patients-treated population (APT). As outlined in the table below, the proportion of subjects with insufficient serum 25 hydroxyvitamin D levels (<15 ng/mL) was significantly lower in the alendronate/vitamin D_3 group (0.11) when compared to the alendronate alone group (0.32) after 15 weeks of therapy ($p<0.001$). The relative risk (alendronate/ vitamin D_3 versus alendronate) was 0.36 ($p<0.001$) with 95% CI of (0.27, 0.48).

Study P227: Proportion of Subjects with Low 25-OH Vitamin D Levels (APT)				
	Aln+VitD		**Aln**	
N	**360**		**357**	
N, APT	357		351	
	<15ng/mL	**<9ng/mL**	**<15ng/mL**	**<9ng/mL**
At baseline; n (proportion)	76 (0.21)	0	75 (0.21)	0
At Week 15; n (proportion)	41 (0.11)	4 (0.01)	112 (0.32)	46 (0.13)
Vitamin D < 15 ng/mL				
Relative Risk	0.36			
95% CI	0.27 , 0.48			
p-value	< 0.001			
Vitamin D < 9 ng/mL				
Relative Risk	0.09			
95% CI	0.03 , 0.23			
p-value	< 0.001			

COMMENT: It should be noted that, while no subjects were vitamin D deficient at baseline, 4 (1%) subjects in the alendronate/vitamin D_3 combination tablet group developed levels consistent with vitamin D deficiency (< 9 ng/mL) despite the vitamin D_3 supplementation.

Change in 25 hydroxyvitamin D Level: As outlined in the table below, baseline 25 hydroxyvitamin D levels were similar between the two treatment groups. Subjects in the alendronate/vitamin D_3 group increased 25 hydroxyvitamin D by 1.2 ng/mL, compared with the alendronate only group which had a decrease in 25 hydroxyvitamin D levels of 3.4 ng/mL. The least-squares mean difference was 4.6 ($p<0.001$). In the subgroup of patients with vitamin D insufficiency at baseline, the increase in 25 hydroxyvitamin D levels was 3.7 ng/mL in the alendronate/vitamin D_3 group versus a decrease of 1.7 ng/mL in the alendronate alone group. Smaller increases were seen in subjects considered vitamin D sufficient. In fact, subjects with vitamin D levels >25 ng/mL at baseline had decreased levels of 25 hydroxyvitamin D at Week 15. The alendronate/vitamin D_3 group had an absolute change of -2.2 ng/mL versus the alendronate only group with an absolute change of -6.1 ng/mL.

Study P227: 25-OH Vitamin D Level (APT)		
	Aln+VitD	**Aln**
N	**360**	**357**
N, APT	357	351
Vitamin D, baseline ng/mL (±SD)	22.2 ± 9.0	22.1 ± 9.4
Vitamin D, Week 15ng/mL (±SD)	23.1 ± 7.9	18.4 ± 8.7
Absolute Change (95% CI)	1.2 (0.6 , 1.8)	-3.4 (-4.0 , -2.8)
LS Mean Difference	4.6	
95% CI	4.0 , 5.3	
p-value	< 0.001	
Subgroup, Baseline D < 15, n	76	75
Vitamin D, baseline ng/mL (±SD)	12.1 ± 1.7	12.1 ± 1.7
Vitamin D, Week 15cng/mL (±SD)	15.8 ± 3.9	10.4 ± 4.0
Absolute Change (±SD)	3.7 ± 3.7	-1.7 ± 3.4
Subgroup, Baseline D 15 – 25, n	158	166
Vitamin D, baseline ng/mL (±SD)	19.6 ± 2.8	19.6 ± 3.0
Vitamin D, Week 15cng/mL (±SD)	21.5 ± 5.2	16.4 ± 5.4
Absolute Change (±SD)	1.9 ± 4.9	-3.2 ± 4.5
Subgroup, Baseline D > 25, n	123	110
Vitamin D, baseline ng/mL (±SD)	31.7 ± 7.7	32.8 ± 8.6
Vitamin D, Week 15cng/mL (±SD)	29.6 ± 7.6	26.7 ± 8.1
Absolute Change (±SD)	-2.2 ± 5.6	-6.1 ± 5.1

COMMENT: it is concerning that in subjects with 25 hydroxyvitamin D levels > 25ng/mL at baseline, there was a decrease in the mean level by Week 15. Many experts advocate a 25 hydroxyvitamin D level of 30 ng/mL or above for sufficiency. After 15 weeks of therapy, 61% of subjects in the alendronate/vitamin D_3 combination tablet group had 25 hydroxyvitamin D levels that did not exceed 25ng/mL (compared to 78% in the alendronate only group) while 78% of subjects in the alendronate/vitamin D_3 combination tablet group had 25 hydroxyvitamin D levels less than 30ng/mL (compared to 85% in the alendronate only group).

Overall, the 25 hydroxyvitamin D levels achieved by Week 15 appear low when compared to other published studies (see table below). One difficulty in comparing studies with regard to the effect of supplementation on 25 hydroxyvitamin D levels is the complexity of the laboratory measurement itself and the significant variability between laboratory methodologies. That said, the differences are striking. The reason for the differences is not clear.

Effect of Vitamin D_3 Supplementation on 25 Hydroxyvitamin D levels					
			25 hydroxyvitamin D level (ng/mL)		
Study	**Age**	**Vitamin D_3 dose**	**baseline**	**follow-up**	**Duration**
Protocol 227	67	2800 weekly	22.2	23.1	15 weeks
Protocol 227**	68	2800 weekly	12.1	15.8	15 weeks
Chel, 1998	85	400 daily	9.2	24	3 months
Lips, 1996	84	400 daily	8	23	3 months
McCauley, 1998	76	400 daily	10	17.4	6 months
Lips, 2001	67	400-600 daily	28.4	37.0	6 months
Lips, 1996	80	400 daily	10.8	24.8	12 months

Effect of Vitamin D_3 Supplementation on 25 Hydroxyvitamin D levels					
			25 hydroxyvitamin D level (ng/mL)		
Study	**Age**	**Vitamin D_3 dose**	**baseline**	**follow-up**	**Duration**
Peacock, 2000	76	600 daily	24.2	47.6	12 months
Dawson-Hughes, 1997	70	700 daily	28.7	44.8	36 months
Pfiefer, 2001	75	800 daily	10.3	25.9	2 months
Freaney, 1993	74	800 daily	2.4	16.4	1 months
Sebert, 1995	83	800 daily	2.6	14.6	6 months
Chapuy, 1996	86	800 daily	16	40	6 months
Veith, 2001	42	1000 daily	17.3	27.5	5 months
Veith, 2001	40	4000 daily	15.1	38.6	5 months
** subset of subjects with baseline 25OH D levels < 15ng/mL					

Vitamin D Shift Table: As outlined in the table below, when evaluating patients who shifted 25 hydroxyvitamin D status, for subjects in the alendronate/vitamin D_3 group with baseline serum 25 hydroxyvitamin D levels in the insufficient range (<15ng/mL), 62% shifted in the higher ranges (>15 ng/mL). Subjects in the alendronate only group who began with baseline serum 25 hydroxyvitamin D levels in the insufficient range (<15ng/mL), only 16% shifted in the higher ranges (>15 ng/mL). It must also be noted that 4.3% of subjects in the alendronate/vitamin D_3 group who began with sufficient 25 hydroxyvitamin D levels shifted into the insufficient range by Week 15, compared to 17.8% in the alendronate only group.

Study P227: Vitamin D Shift Table (APT)						
	Aln+VitD			**Aln**		
N	**360**			**357**		
N, APT	357			351		
Baseline Vitamin D	**Week 15 Vitamin D**			**Week 15 Vitamin D**		
	Total	**< 15**	**> 15**	**Total**	**< 15**	**> 15**
< 15ng/mL	76	29 (38.2)	47 (61.8)	75	63 (84.0)	12 (16.0)
15-25 ng/mL	158	10 (6.3)	148 (93.7)	166	48 (28.9)	118 (71.1)
> 25ng/mL	123	2 (1.6)	121 (95.7)	110	1 (0.9)	109 (99.1)

COMMENT: Overall, 6% subjects with baseline 25 hydroxyvitamin D levels of 15 – 25 ng/mL and 2% of subjects with baseline levels > 25 ng/mL shifted into the insufficient range despite receiving the alendronate/D_3 combination tablet. While the occurrence is clearly lower than what is seen in the alendronate only group, it is a sufficient number to raise concern.

Markers of Calcium Metabolism: The table below outlines the changes seen in markers of calcium metabolism. Alendronate's action as a bone antiresorptive agent has been well described. Serum calcium levels fell in both treatment groups. Although the decrease was smaller in the alendronate/D_3 group the difference was not significant. As well, serum phosphorus levels fell in growth both groups. Parathyroid hormone levels increased in both groups with a statistically significant difference of -10.43 (p= 0.004). Twenty-four-hour urine calcium levels decreased in both groups and it was no significant difference between treatment groups.

Study P227: Markers of Calcium Metabolism (PP)				
	Aln+VitD		**Aln**	
N	**360**		**357**	
N, PP	325		319	
	Baseline	**Week 15**	**Baseline**	**Week 15**
Serum Calcium	9.49	9.43	9.48	9.38
Percent Change	-0.87		-1.38	
Treatment Difference (95% CI)	0.51 (-0.08 , 1.10)			
p-value	0.09			
Serum Phosphate	3.58	3.47	3.61	3.45
Percent Change	-2.37		-3.60	
Treatment Difference (95% CI)	1.22 (-0.64 , 3.09)			
p-value	0.198			
24hour Urine Calcium	172.58	144.19	170.61	132.73
Percent Change	-23.00		-28.41	
Treatment Difference (95% CI)	5.41 (-1.08 , 11.91)			
p-value	0.102			
Parathyroid Hormone	47.35	52.47	45.46	54.65
Percent Change	13.90		24.33	
Treatment Difference (95% CI)	-10.43 (-17.57 , -3.30)			
p-value	0.004			

COMMENT: The changes noted in serum calcium and PTH suggest that the addition of vitamin D_3 in the combination tablet may confer a protective effect against the expected decrease in serum calcium and subsequent increase in PTH level seen with alendronate therapy.

Bone Biomarkers: Bone specific alkaline phosphatase (BSAP) and urinary N-telopeptide (NTx) levels were evaluated to assess bone turnover between the two groups. As outlined in the table below, there was no significant difference between the alendronate/D_3 group and the alendronate group with regard to bone formation (serum osteocalcin -27% in the alendronate/D_3 group vs. -25% in the alendronate only group) or bone resorption (urinary NTx -53.40% in the alendronate/D_3 group vs. -53.27% in the alendronate only group).

Study P227:Bone Biomarkers (PP)				
	Aln+VitD		**Aln**	
N	**360**		**357**	
N, PP	325		319	
	Baseline	**Week 15**	**Baseline**	**Week 15**
Bone Specific Alkaline Phosphatase	28.29	20.89	28.34	21.60
Percent Change	-27.21		-25.16	
Treatment Difference (95% CI)	-2.06 (-4.91 , 0.80)			
p-value	0.157			
Urinary NTx	62.93	29.97	63.96	30.89

Study P227:Bone Biomarkers (PP)		
	Aln+VitD	Aln
Percent Change	-53.40	-53.27
Treatment Difference (95% CI)	-0.13 (-3.67 , 3.41)	
p-value	0.942	

Safety

Adverse Events Rates: One subject in the alendronate only group received no study medication and is not included in the safety population..

Study P227: Adverse Event Rates (Safety)			
	Aln+VitD	Aln	Total
N	360 (%)	357 (%)	717 (%)
One or more adverse event	215 (59.7)	210 (58.8)	425 (59.3)
Deaths	0	0	0
Serious adverse events	7 (1.9)	15 (4.2)	22 (3.1)
Withdrawal due to serious AE	1 (0.3)	2 (0.6)	3 (0.4)
Withdrawal due to adverse event	18 (5.0)	17 (4.8)	35 (4.9)

Exposure: In this study, subjects received 70mg alendronate or 70mg alendronate and 2800IU vitamin D_3 weekly. The mean number of weeks on study drug was 14.7 for the alendronate only group and 14.8 for the alendronate/vitamin D_3 group.

Study P227: Exposure			
	Aln+VitD	Aln	Total
N	360	356	716
Mean number of weeks on drug	14.8	14.7	
≤ 1 week	7	3	10
> 1 to ≤ 5 weeks	7	9	16
> 5 to ≤ 10 weeks	8	11	19
> 10 to ≤ 15 weeks	152	147	299
> 15 weeks	186	186	372

A total of 3 subjects had an overdose of study drug in Protocol 227. One subject in the alendronate only group took 5 study tablets in a period of time when she should have taken 4; one subject in the alendronate/vitamin D_3 group took study therapy 4 days in a row and then 2 days in a row for a total of 6 doses in seven days; and one subject in the alendronate/vitamin D_3 group took 2 tablets from the same bottle on the same day. None of the patients experienced an adverse event.

Deaths: No deaths were reported in this study.

Serious Adverse Events: Overall, 22 (3.1%) subjects (7 (1.9%) subjects in the alendronate/vitamin D_3 group and 15 (4.2%) subjects in the alendronate only group) experienced a serious adverse event.

Study P227: Serious Adverse Events						
Patient	Age	Sex	Event	Onset (day)	Action	Days off drug
Alendronate + D Group						
2159	55	F	pancreatic carcinoma	45	d/c	
2236	71	F	basal cell carcinoma	51	cont	1
2474	68	F	blepharitis / trichiasis	4	cont	3
2332	67	F	depression	36	cont	5
2334	67	F	upper limb fracture	60	cont	3
2500	88	F	traumatic hematoma	65	cont	2
2502	80	F	basal cell carcinoma	63	cont	0
Alendronate only Group						
2020	82	M	thrombosis/ PE	87	cont	2
1034	68	F	syncope/abdo pain/vomiting	2	d/c	
2682	66	F	head injury/contusion/ rib fx	88	cont	3
2694	55	F	retinal detachment	83	cont	4
2469	69	F	gastric ulcer/gastric cancer	73	d/c	
2246	85	F	anemia	62	cont	2
1317	70	F	anemia	49	cont	6
2366	53	M	tibia/fibula fracture	69	cont	6
2526	70	F	cerebrovascular accident	46	cont	3
1447	66	F	respiratory tract infection	95	cont	3
2484	78	F	squamous cell skin Ca	71	cont	1
2506	82	F	myocardial infraction	55	cont	5
2273	68	F	transient ischemic attack	26	cont	6
1451	82	F	atrial fibrillation	86	cont	1
1326	65	F	bronchopneumonia	60	cont	5

Adverse Events Leading to Withdrawal: A total of 35 (4.9%) subjects withdrew from the study due to adverse events. Withdrawals were evenly distributed between the two treatment groups [18(5.0%) subjects in the alendronate/vitamin D_3 group and 17 (4.8%) subjects in the alendronate only group]. As outlined in the table below, gastrointestinal adverse events followed by musculoskeletal adverse events and nervous system adverse events were the most reason for withdrawal in both groups.

Study P227: Adverse Events Leading to Withdrawal			
	Aln+VitD	**Aln**	**Total**
N	360 (%)	357 (%)	717 (%)
Total	**18**	**17**	**35**
Gastrointestinal	8 (2.2)	9 (2.5)	17 (2.4)
Hepatobiliary	0	1 (0.3)	1 (0.1)
Body as a Whole	1 (0.3)	1 (0.3)	2 (0.3)
Infections	1 (0.3)	0	1 (0.1)

Study P227: Adverse Events Leading to Withdrawal			
	Aln+VitD	Aln	Total
Metabolic	1 (0.3)	0	1 (0.1)
Musculoskeletal	3 (0.8)	3 (0.8)	6 (0.8)
Nervous	2 (0.6)	2 (0.6)	4 (0.6)
Neoplasms	1 (0.3)	1 (0.3)	2 (0.3)
Respiratory	1 (0.3)	0	1 (0.1)
Skin and Subcutaneous	1 (0.3)	1 (0.3)	2 (0.3)
Vascular	1 (0.3)	0	1 (0.1)
The same patient is counted only once in a category, but may appear in more than one category			

Adverse Events: As outlined in the section below, the overall incidence of AEs in Protocol 227 was comparable between the two treatment groups and occurred in 59% of study subjects. The most common adverse event categories were infectious, gastrointestinal and musculoskeletal. The most common clinical adverse events were nasopharyngitis, arthralgia, back pain, and headache.

Study P227: Adverse Events			
	Aln+VitD	Aln	Total
N, safety population	**360**	**357**	**717**
Total subjects with AEs	**215 (59.7)**	**210 (58.8)**	**425 (59.3)**
Body as a whole	20 (5.6)	19 (5.3)	39 (5.4)
Gastrointestinal	62 (17.2)	76 (21.3)	138 (19.2)
Injury*	21 (5.8)	18 (5.0)	39 (5.4)
Nervous	28 (7.8)	20 (5.6)	48 (6.7)
Cardiac	4 (1.1)	8 (2.2)	12 (1.7)
Hepatobiliary	1 (0.3)	1 (0.3)	2 (0.3)
Neoplasms	4 (1.1)	3 (0.8)	7 (1.0)
Respiratory	17 (4.7)	10 (2.8)	27 (3.8)
Endocrine/Metabolic	5 (1.4)	9 (2.5)	14 (2.0)
Musculoskeletal	59 (16.4)	73 (20.4)	132 (18.4)
Infectious	91 (25.3)	76 (21.3)	167 (23.3)
Immune	5 (1.4)	1 (0.3)	6 (0.8)
Blood and Lymphatic	1 (0.3)	4 (1.1)	5 (0.7)
Skin and Appendages	17 (4.7)	18 (5.0)	35 (4.9)
Renal / Urinary Disorders	4 (1.1)	4 (1.1)	8 (1.1)
Reproductive	2 (0.6)	2 (0.6)	4 (0.6)
Vascular Disorders	17 (4.7)	11 (3.1)	28 (3.9)
Eye Disorders	6 (1.7)	13 (3.6)	19 (2.6)
Hearing / Vestibular	6 (1.7)	8 (2.2)	14 (2.0)
Psychiatric	8 (2.2)	10 (2.8)	18 (2.5)
* including fracture The same patient is counted only once in a category, but may appear in more than one category			

Adverse Events of Special Interest:

Fracture: As outlined in the table below, a total of eight subjects experienced a fracture during the study. All fractures were at nonvertebral sites.

Study P227: Fractures as Adverse Event						
Patient	Age	Sex	Fracture site	Onset (day)	T score	Comment
Alendronate + D Group						
2334	67	F	upper limb fracture (elbow)	60	-2.7	on Ca, T4
1359	63	F	hand fracture	22	-3.3	on Ca + D
2584	83	F	rib fracture	4	-4.0	on Ca + D
2696	57	F	radial fracture	94	-3.3	on Ca, ERT
Alendronate only Group						
2366	53	M	tibia/fibula fracture	69	-3.4	no Ca
2098	54	F	foot fracture	105	-2.5	on Ca
2313	69	F	calcaneus fracture	107	-3.2	on Ca
2682	66	F	rib fracture	88	-1.8	on Ca

GI Adverse Events: Oral, nitrogen-containing bisphosphonates are well known to cause gastroesophageal irritation. In protocol 227, a total of 102 subjects experienced adverse events related to the gastrointestinal tract which may be related to known bisphosphonate effects. The most common adverse events were abdominal pain, dyspepsia and nausea. Event rates were slightly higher in the alendronate only group.

Study P227: Gastrointestinal Adverse Events			
	Aln+VitD	**Aln**	**Total**
N, safety population	**360**	**357**	**717**
Total subjects with AEs	**47**	**55**	**102**
Abdominal pain/discomfort	18 (5.0)	25 (7.0)	43 (6.0)
Diarrhea	7 (1.9)	6 (1.7)	13 (1.8)
Dyspepsia/ GERD	12 (3.3)	15 (4.2)	27 (3.8)
Esophagitis/Esoph erosion	0	2 (0.6)	2 (0.3)
Gastritis	2 (0.6)	3 (0.8)	3 (0.4)
Gastric Ulcer	0	1 (0.3)	1 (0.1)
Gastric disorder, NOS	0	1 (0.3)	1 (0.1)
Nausea	14 (3.9)	11 (3.1)	25 (3.5)
Vomiting	4 (1.1)	7 (2.0)	11 (1.5)

Musculoskeletal Adverse Events: An increased incidence of bony pain, noted primarily in post-marketing, spontaneous adverse event reporting, has been observed with bisphosphonate use. Overall, musculoskeletal pain symptoms occurred in 61 subjects (26 in the alendronate/vitamin D_3 group and 35 in the alendronate only group). Specifically, bone pain occurred in 6 subjects, with a higher incidence in the alendronate only group (5 subjects, compared to 1 subject in the alendronate/vitamin D_3 group).

Study P227: Musculoskeletal Adverse Events			
	Aln+VitD	**Aln**	**Total**
N, safety population	**360**	**357**	**717**
Total subjects	**26**	**35**	**61**
Back pain	15 (4.2)	15 (4.2)	30 (4.2)
Bone pain	1 (0.3)	5 (1.4)	6 (0.8)
Chest wall pain	1 (0.3)	2 (0.6)	3 (0.4)
Musculoskeletal pain	0	1 (0.3)	1 (0.1)
Neck pain	5 (1.4)	5 (1.4)	10 (1.4)
Pain in extremity	8 (2.2)	13 (3.6)	21 (2.9)

Eye Adverse Events: An increased incidence of inflammatory eye diseases, such as uveitis and scleritis, has been reported with bisphosphonate use. Overall, 19 [6 (1.7%) subjects in the alendronate+D group and 13 (3.6%) subjects in the alendronate only group] subjects experienced adverse events related to the eye. Symptoms related to eye inflammation (including pain, erythema, pruritis, conjunctivitis, blepharitis, scleritis and iritis) occurred in 10 subjects. Events are outlined in the table below.

Study P227: Ocular Adverse Event					
Patient	Age	Sex	Event	Onset (day)	Comment
Alendronate + D Group					
2115	71	F	Eye pain	20	
2421	68	F	Eye pruritis	40	
2474	68	F	Blepharitis	4	
2510	71	F	Blepharo-conjunctivitis	54	
Alendronate only Group					
1360	58	F	Scleritis	50	
1360	58	F	Conjunctivitis	68	
2002	58	F	Conjunctivitis	69	
2114	53	M	Iritis	54	
2309	70	F	Iritis	49	
2378	66	F	Eye pain	44	
2602	79	F	Conjunctivitis	4	

Laboratory

Laboratory Adverse Events: Overall, 81 subjects [61(16.9%) subjects in the alendronate/D_3 group and 20 (5.6%) subjects in the alendronate only group] had laboratory abnormalities reported as adverse events. As outlined in the table below, the most common abnormality was decreased 25-hydroxy vitamin D levels. Decreased vitamin D levels occurred in 46 subjects in the alendronate only group and 4 subjects in the alendronate/vitamin D group, and accounts for the imbalance of events between the two treatment arms. Aside from abnormalities in 25 hydroxyvitamin D levels, urine dipstick positive for white blood cells was the most common

abnormality and occurred in 2.0% of subjects in the alendronate/vitamin D_3 group and 2.5% of subjects in the alendronate only group.

Study P227: Laboratory Adverse Events

	Aln+VitD	Aln	Total
N, safety population	**360**	**357**	**717**
Total subjects with AEs	**17**	**61**	
25-OH vitamin D, decreased	4	46	50
Blood calcium, decreased	2	0	2
Urine calcium, decreased	0	1	1
Urine calcium, increased	2	2	4
Potassium, increased	0	1	1
Glucose, increased	0	2	2
SGOT and/or SGPT increased	1	2	3
Alkaline phosphatase, increased	1	0	1
Cholesterol, increased	0	1	1
Ferritin, decreased	0	1	1
Homocysteine, increased	0	1	1
WBC, decreased	0	2	2
Platelets, decreased	2	1	3
Urinalysis, abnormal	5	7	12

A total of 8 subjects withdrew prematurely from the study due to decreased 25-hydroxy vitamin D levels, all in the alendronate only arm of the study. As outlined in the table below, most of these discontinued subjects had 25-OH Vitamin D levels below 15 ng/mL at study onset.

Study P227: Withdrawals due to Low Vitamin D Levels

Patient	Age	Sex	W/D day	Vitamin D Level (ng/mL)				Comment
				baseline[1]	Wk 5	Wk 10	Wk 15	
1009	54	F	34	10				*off drug
1097	69	F	41	9				*off drug
1161	82	F	43	13				*off drug
1274	48	F	106	9				
1309	73	F	71	10				*off drug
2113	64	F	71	14				*off drug
2201	73	F	78	16				*off drug
2233	69	F	43	16				*off drug

[1] average of the 2 pre-randomization values

Laboratory Abnormalities Outside the Predefined Limits of Change: The table below outlines the marked laboratory abnormalities. There were no clinically significant differences between treatment groups with the exception of 25 hydroxyvitamin D levels.

Study P227: Laboratory Abnormalities Outside Predefined Limits of Change			
	Aln+VitD	Aln	Difference %
N, safety population	**360**	**357**	**(95% CI)**
25-OH Vitamin D level			
Value < 9	4 (1.1)	46 (13.1)	-12.0 (-16.0,-8.4)
Serum Calcium (mg/dL)			
Value < 8	1 (0.3)	2 (0.6)	-0.3 (-1.8,1.1)
Value < 8.5	10 (2.8)	9 (2.6)	0.2 (-2.3,2.8)
Value > 10.5	5 (1.4)	2 (0.6)	0.8 (-0.9,2.7)
Urine Calcium (mg/24hr)			
Increase ≥ 25%	62 (18.1)	55 (16.5)	1.6 (-4.1,7.3)
Value > 300mg/24hr	40 (11.7)	28 (8.4)	3.3 (-1.3,7.9)
Value < 50mg/24hr	22 (6.4)	29 (8.7)	-2.3 (-6.4,1.8)
Serum Phosphate (mg/dL)			
Value < 2.0	2	2 (0.6)	-0.6 (-2.1,0.6)
Decrease ≥ 30% and value < LLN (2.50)	4 (1.1)	7 (2.0)	-0.9 (-3.1,1.1)
Increase ≥ 30% and value > ULN (4.50)	2 (0.6)	2 (0.6)	-0.0 (-1.6,1.5)
Sodium (meq/L)			
Decrease ≥ 10 and value < LLN (133)	1 (0.3)	0	0.3 (-0.8,1.6)
Increase ≥ 10 and value > ULN (145)	1 (0.3)	0	0.3 (-0.8,1.6)
Potassium (meq/L)			
Increase ≥ 0.5 and value > ULN (5.00)	12 (3.5)	11 (3.3)	0.2 (-2.7,3.1)
Blood Urea Nitrogen (mg/dL)			
Increase ≥ 50%	17 (4.8)	11 (3.2)	1.6 (-1.4,4.8)
Increase ≥ 50% and baseline >ULN	0	1 (0.3)	-0.3 (-1.6,0.8)
AST, SGOT (IU/L)			
Increase ≥ 50% and value > ULN (25.00)	4 (1.1)	5 (1.5)	-0.4 (-2.3,1.6)
ALT, SGPT (IU/L)			
Increase ≥ 50% and value > ULN (25.00)	2 (0.6)	4 (1.2)	-0.6 (-2.4,1.1)
Alkaline Phosphatase (IU/L)			
Increase ≥ 50% and value > ULN (90.00)	2 (0.6)	2 (0.6)	-0.0 (-1.6,1.5)
WBC (10^3/μL)			
Decrease ≤ 20% and value < LLN (4.80)	14 (4.1)	6 (1.8)	2.3 (-0.3,5.1)
Value < LLN (4.80)	75 (21.6)	84 (24.6)	-3.0 (-9.3,3.3)
Increase ≥ 20% and value > ULN (10.80)	3 (0.9)	1 (0.3)	0.6 (-0.9,2.2)
Hematocrit (%)			
Decrease ≤ 20% and value < LLN (42)	0	1 (0.3)	-0.3 (-1.6,0.8)
Hemoglobin (gm/dL)			
Decrease ≤ 20% and value < LLN (14.0)	0	1 (0.3)	-0.3 (-1.6,0.8)
Platelets (10^3/μL)			
Decrease ≤ 25% and value < LLN (150)	1 (0.3)	2 (0.6)	-0.3 (-1.8,1.1)

As outlined in the table below, there was no clinically significant change in laboratory parameters from beginning to end of study. The change in alkaline phosphatase can be attributed to the action of alendronate on bone.

Study P227: Laboratory Mean Change from Baseline to Week 15 (APT)						
	Aln+VitD			Aln		
N, safety population	360			357		
	Base	Wk 15	%chng	Base	Wk 15	%chng
Sodium (meq/L)	142.15	142.20	-0.01	142.31	141.90	-0.40
Potassium (meq/L)	4.38	4.38	-0.00	4.42	4.38	-0.02
Creatinine (mg/dL)	0.90	0.91	0.01	0.91	0.91	0.01
AST, SGOT (IU/L)	15.76	15.10	-0.59	15.47	15.59	0.10
ALT, SGPT (IU/L)	13.08	12.31	-0.79	12.71	13.10	0.35
Alkaline Phosphatase (IU/L)	57.02	47.10	-9.43	57.03	48.65	-7.95
WBC (103/µL)	5.69	5.79	0.14	5.73	5.81	0.05
Hematocrit (%)	39.77	39.85	0.16	39.84	40.04	0.26
Hemoglobin (gm/dL)	13.48	13.46	0.00	13.49	13.50	0.03
Platelets (103/µL)	240.24	241.26	1.14	247.76	246.19	0.15
AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase						

Hypercalcemia: Hypercalcemia is an important side effect of over-replacement with vitamin D. Nine subjects (2 in the alendronate only group and 7 in the alendronate/vitamin D_3 group) had at least one calcium level that met criteria for hypercalcemia (> 10.5 mg/dL). There was no consistent pattern in the elevations seen. The highest calcium level in any subject was 10.9 mg/dL.

Protocol 227: Serum Calcium Levels of Subjects with Hypercalcemia							
			Serum calcium level (mg/dL)				
AN	Age	Sex	Visit 1 Screen	Visit 3 Baseline	Visit 5 Day 35	Visit 6 Day 71	Visit 7 Final
Alendronate Only Group							
2098	54	F	10.3	10.3			
2511	70	F	10.0	10.2			
Alendronate + D Group							
1025	74	F	9.3	9.9			
2136	60	F	10.8	10.5		d/c'd, pt moved	
2232	76	F	10.7	10.2			
2287	66	F	9.5	9.6			
2354	63	F	10.6	10.7		d/c'd, AE – hot flush	
2359	66	F	10.1	9.7			
2551	54	F	10.6	10.5			

Hypercalciuria: Hypercalciuria is also an important side effect of over-replacement with vitamin D. As outlined in the table below, 18.1% of subjects in the alendronate/vitamin D_3 group had an increase in urine calcium greater than 25% over baseline compared to 16.5% of the alendronate only group. As well, 11.7% of subjects in the alendronate/vitamin D_3 group had urine calcium greater than 300mg/day, compared to 8.4% in the alendronate only group. The percentage of subjects with a urine calcium that was both >300 mg/day and increased >25% over baseline was similar in both treatment groups. The occurrence of hypercalciuria did not change when analysis was performed based on daily calcium intake.

Study P227: Proportion of Patients with Hypercalciuria (APT)		
	Aln+VitD	**Aln**
N	**360**	**357**
Increase ≥ 25%	62 (18.1)	55 (16.5)
Level > 300mg/day	40 (11.7)	28 (8.4)
Increase ≥ 25% + Level > 300mg/day	14 (4.1)	14 (4.2)
Calcium Intake 34-805 mg/day	170	161
	7 (4.1)	7 (4.3)
Calcium Intake 805-2126 mg/day	163	167
	7 (4.3)	7 (4.2)

Vital Signs: As outline in the table below, there were no clinically significant changes in vital signs (systolic and diastolic blood pressure, heart rate, or body weight) during the study.

Study P227: Vital Signs Mean Change from Baseline to Week 15 (APT)						
	Aln+VitD			**Aln**		
N, safety population	**360**			**357**		
	Base	**Wk 15**	**chng**	**Base**	**Wk 15**	**chng**
Systolic blood pressure (mmHg)	131.30	130.02	1.01	132.62	131.26	-1.34
Diastolic blood pressure (mmHg)	77.52	76.37	-1.01	77.68	76.94	-0.69
Heart rate (bpm)	70.23	70.85	1.10	69.30	70.90	1.72
Weight (kg)	62.95	63.50	0.62	64.60	64.95	0.61

A total of 17 subjects reported adverse events related to vital signs, as outlined in the table below,. None were serious adverse events. The events were evenly distributed between the groups.

Study P227: Clinical Adverse Events			
	Aln+VitD	**Aln**	**Total**
N, safety population	**360**	**357**	**717**
Blood pressure, increased	2	2	4
Heart rate irregular	1	1	2
Cardiac murmur	3	1	4
Intraocular pressure increased	0	1	1
Weight increased	1	4	5
Weight decreased	1	0	1

Discussion and Conclusions: In this study, after 15 weeks of therapy, the proportion of subjects with insufficient serum 25-hydroxyvitamin D levels (<15 ng/mL) was significantly lower in the combination alendronate/vitamin D_3 group when compared to the alendronate alone group. The increase in 25 hydroxyvitamin D levels seems very small in comparison (22.2 ng/mL at baseline to 23.1 ng/mL at 15 weeks) to other studies. In 65% of subjects with the alendronate/vitamin combination tablet, the mean 25 hydroxyvitamin D level did not exceed 25 ng/mL at a time when many experts advocate a level of 30 ng/mL or above for sufficiency. As well, in subjects with 25 hydroxyvitamin D levels > 25ng/mL at baseline, there was a decrease in the mean level by Week 15. Overall, 6% subjects with baseline 25 hydroxyvitamin D levels of 15 – 25 ng/mL

and 2% of subjects with baseline levels > 25 ng/mL shifted into the insufficient range despite receiving the alendronate/D_3 combination tablet. Overall, these data suggest that the current 2800IU weekly dose of vitamin D_3 is insufficient to sustain adequate 25 hydroxyvitamin D levels in some subjects.

Both treatment groups received alendronate, with similar decreases in bone biomarkers. As well, both groups had decreases in serum calcium and increases in serum PTH although to a lesser extent in the combination alendronate/vitamin D_3 group. This suggests that the addition of vitamin D_3 in the combination tablet may confer a protective effect against the expected decrease in serum calcium and subsequent increase in PTH level seen with alendronate therapy.

In this study, there were no unexpected safety findings uncovered. There was an imbalance between the alendronate only group and the alendronate/vitamin D_3 group in the number of subjects who withdrew due to laboratory adverse events. All of the withdrawals occurred in the alendronate group and were due to low 25 hydroxyvitamin D levels. This was not unanticipated, due to the lack of vitamin D supplementation in the alendronate only group and acts to stress the importance of adequate vitamin D nutrition.

The upper limit of normal intake for vitamin D is considered 2000 IU/day. While the vitamin D dosing with the combination alendronate/vitamin D_3 weekly tablet exceeds this amount on the day of dosing, there was no evidence of persistent hypercalcemia or hypercalciuria in study subjects.

10.1.2 Protocol 226: A 2-part, open-label, randomized, crossover study to evaluate the bioequivalence of the 70mg alendronate/2800IU vitamin D_3 final-market combination tablet to a 70mg alendronate marketed tablet, and the relative bioavailability of vitamin D_3

Objectives: The objectives of this study were:

- Part I: To compare the urinary excretion of alendronate following administration of a 70mg alendronate/2800IU vitamin D_3 final-market combination tablet relative to a 70mg alendronate market tablet.
- Part II: To compare the pharmacokinetic parameters (AUC0-120 hr, Cmax) of vitamin D_3 administered as the 70-mg alendronate/2800-IU vitamin D_3 final-market combination tablet relative to a 2800-IU vitamin D_3 tablet.

Study Design: This was an open-label, randomized, 2-part, 2-period, crossover study in 244 healthy non-pregnant women and men age 18 to 65. The study was conducted in 2 parts (Parts I and II) with each consisting of a 2-period, crossover design. Each subject participated in one part of the study only (i.e., each subject participated only in Part I or only in Part II). Subjects entered into the study sequentially within each part of the study. Part I included Treatments A and B, and Part II included Treatments A and C, as outlined in the table below.

Study P226: Treatments	
Treatment	
A	single dose of a 70-mg alendronate/2800-IU vitamin D_3 final-market combination tablet
B	single dose of a 70-mg alendronate market tablet
C	a single dose of a 2800-IU vitamin D_3 tablet (containing the placebo excipients to alendronate)

Population: The intended study population was healthy adults between the ages of 18 and 65 years of age.

Inclusion Criteria

- Subject was a male or a non-pregnant female from 18 to 65 years of age. Female subjects of childbearing potential could not be nursing and must have demonstrated a serum β-hCG level consistent with the nongravid state at the screening visit. Female subjects of non-childbearing potential must have demonstrated an FSH level consistent with the postmenopausal state or have a documented history of surgical sterilization (e.g., status post hysterectomy, tubal ligation)
- Subjects of childbearing potential agreed to use an appropriate method of contraception (i.e., abstinence or double-barrier method) (Note: Oral contraception and other hormonal methods of contraception were not allowed) for at least 14 days prior to the study and continuing for at least 14 days following the last study visit.
- Subject had a Body Mass Index (BMI) ≤30 kg/m2
- Subject was judged to be in good health on the basis of medical history, physical examination, and laboratory studies
- Subject understood the procedures and agreed to participate in the study program
- For subjects in Part II only: Subject was willing to limit direct sunlight exposure during the course of the study (e.g., avoid sunbathing, tanning salons) and apply sunscreen to exposed skin if anticipating exposure to direct sunlight for an extended period of time (1 hour)

Exclusion Criteria

- Subject was mentally or legally incapacitated
- Subject had received prior bisphosphonate treatment within 3 months for any reason
- Subject had a history of allergy, hypersensitivity, or an intolerance to diagnostic testing with any bisphosphonate, vitamin D product, or component of these products
- Subject currently used (within 2 weeks) or was planning to use any prescribed or nonprescribed drugs on a regular basis (including over-the-counter drugs, herbal remedies, such as St. John's Wort, or nutritional supplements, such as multivitamins). Subjects could use a stable dose of hormone replacement therapy (constant dose), HMG-CoA reductase inhibitor, or prophylactic aspirin
- Subject had significant abnormalities on prestudy clinical examination or laboratory measurements which were obtained within 3 weeks of dosing
- Subject had any genitourinary or other medical or psychological problem which would preclude accurate collections of urine samples
- Subject had a recent history (within the past year) of peptic ulceration, symptomatic gastroesophageal reflux, abnormalities of the esophagus or stomach which delay emptying such as stricture or achalasia, or other gastroesophageal disease or symptoms requiring regular use (i.e., >2 times per week) of antacids, H2 antagonists, or antipeptic medications (H2 blockers, sucralfate, anticholinergics, omeprazole or other proton pump inhibitors)
- Subject had a history of other major gastrointestinal (GI) disease

- Subject was taking thyroid hormone as replacement therapy (unless it is a stable dose for at least 6 months) and was euthyroid based on a normal, sensitive immunoradiometric assay TSH assay
- Subject had substantially reduced renal function defined as serum creatinine >1.5 mg/dL or a creatinine clearance of <80 mL/min, based on the Cockroft- Gault equation, which is as follows (and 0.85 x this value for females):

  CrCl (mL/min) = (140-age) x weight (kg) / 72 x serum creatinine (mg/dL)
- Subject had history of, or evidence for, any metabolic bone disease other than postmenopausal osteoporosis, including but not limited to: Paget's disease, thyroid-related bone disease, osteomalacia, osteogenesis imperfecta; subject had endogenous or exogenous corticosteroid excess (received ≥5 mg prednisone or equivalent daily for >1 month within 1 year of study start); subject had any neoplastic bone disease
- Subject had a history of, or evidence for, significant end-organ disease, i.e., genitourinary, cardiovascular, hepatic, renal, or pulmonary disease, which could pose additional risk to his or her participation in this study. Subject had had a myocardial infarction during the prior year
- Subject was unable to stand or sit upright (at least at a 45° angle) for at least 2 hours

Additional Exclusion Criteria for Part II Only:

- Subject currently used, or had used active vitamin D compounds (e.g., calcifediol, calcitriol, dihydrotachysterol, doxercalciferol, and ergocalciferol), calcium/vitamin D combination supplements (e.g., Viactiv Chews™), and multivitamins containing vitamin D within 10 days prior to dosing.
- Subject had received a high dose of vitamin D3 (>5000 IU) within 4 weeks prior to dosing.
- Subject received regular, prolonged sun exposure and was unable to avoid this sun exposure during the study (e.g., the subjects' employment required them to be outdoors in the sun for extended periods of time).
- Subjects anticipated being unable to avoid prolonged sun exposure (periods >1 hour) and were unwilling to protect themselves from direct sun exposure (e.g., sunscreen, hat) during the study.
- Subject had a 25(OH)-vitamin D level <15 ng/mL at screening.

COMMENT: The inclusion and exclusion criteria appear appropriate. Subjects with gastrointestinal disease, including use of gastric acid reducing medications, were excluded from enrollment. Although subjects taking corticosteroids were excluded, there was no exclusion for other medications affecting the gastrointestinal tract, such as non-steroidal anti-inflammatory drugs.

Study Medication: Each subject in Part I received a single oral dose of 70mg lendronate/2800IU vitamin D_3 combination tablet and a single oral dose of 70mg alendronate in a randomized, crossover fashion. Subjects in Part II received a single oral dose of 70mg alendronate/2800IU vitamin D_3 combination tablet and a single oral dose of a 2800IU vitamin D_3 tablet in a randomized crossover fashion. Doses were administered with 240 mL of plain tap water following an overnight fast and subjects were instructed not to lie down and to remain upright (no less than a 45° angle, sitting or standing) for 2 hours after dosing.

Efficacy Measures

Primary Endpoint, Part I: The primary pharmacokinetic parameter in Part I was total urinary excretion of alendronate from 0 to 36 hours following oral-dose administration.

Primary Endpoint, Part II: The primary pharmacokinetic parameters in Part II were $AUC_{0\text{-}120\ hr}$ and Cmax of vitamin D_3.

Safety Measures: Safety parameters were assessed throughout the study by physical examination, vital signs (blood pressure, heart rate, temperature), laboratory measurements, and adverse event reporting. The safety laboratory measurements included hemoglobin, hematocrit, WBC (total and differential), platelet count, sodium, potassium, fasting glucose, calcium, BUN, creatinine, alkaline phosphatase, SGOT (AST), SGPT (ALT), bilirubin, albumin, and urinalysis by dipstick with microscopic evaluation if positive. A 12-lead electrocardiogram (ECG) was performed at prestudy only.

Study Methods: Subjects were sequestered in the study unit starting with the day prior to each treatment (for Part I this was the evening prior, and for Part II this was 24 hours before treatment administration, prior to the -24-hour predose blood collection), and remained until completion of the pharmacokinetic sampling period (36 hours post-dose in Part I, and 120 hours post-dose in Part II). Doses were administered with 240 mL of tap water after an overnight fast from all food and liquid, except water. Subjects remained fasted until administered a standard meal at 2 hours following dose administration. The order in which each subject received treatments was assigned according to a randomized allocation schedule, and each subject received both treatments within each part of the study. There was a washout interval of at least 12 days between treatment periods within each part of the study.

In Part I, urine was collected starting 2 hours prior to, and over the 36 hours following, dose administration in each period for determination of total urinary excretion of alendronate. Urine collections periods included first morning void, -2 to 0 hours predose, 0 to 8, 8 to 24, and 24 to 36 hours postdose.

In Part II, blood samples were collected for serum vitamin D_3 determination in each period at -24, -18, -12, and -6 hours predose, and 0, 2, 3, 5, 7, 9, 12, 16, 24, 36, 48, 72, 96, and 120 hours postdose.

Withdrawal criteria: Subjects were to be discontinued in the event of an adverse experience that jeopardized their safety and well being.

Statistical Analyses: The bioavailability of alendronate in the 70mg alendronate tablet/2800IU vitamin D_3 combination tablet relative to the 70mg alendronate alone tablet was estimated using the GMR for the total urinary excretion of alendronate from the alendronate/vitamin D_3 combination tablet versus the 70mg alendronate-alone tablet. The relative bioavailability of the 70mg alendronate/2800IU vitamin D_3 combination tablet with respect to 2800IU vitamin D_3 tablet alone was estimated using the GMR (alendronate plus vitamin D_3 / vitamin D_3 alone) for $AUC_{0\text{-}120\ hr}$ and C_{max}.

Hypotheses

1. The oral bioavailability of alendronate as determined by the total urinary excretion of alendronate will be bioequivalent between administration of a 70mg alendronate/2800IU vitamin D_3 final-market combination tablet and the 70mg alendronate market tablet

[geometric mean ratio (GMR) of the combination tablet/alendronate-only tablet will be contained within (0.80, 1.25)].

2. The oral bioavailability of vitamin D_3 as determined by pharmacokinetic parameters ($AUC_{0\text{-}120\ hr}$, C_{max}) will be bioequivalent between administration of a 70mg alendronate/2800IU vitamin D_3 final-market combination tablet and a tablet containing 2800IU vitamin D_3 [the GMR for $AUC_{0\text{-}120\ hr}$ and C_{max}, adjusted for predose concentration, of the combination tablet/2800IU vitamin D_3 only tablet will be contained within (0.80, 1.25)].

Protocol Amendments: The protocol did not require amendments. The data analysis plan was amended because the initial adjustments proposed to control for baseline vitamin D_3 level resulted in a non-physiologic, negative $AUC_{0\text{-}120\ hr}$ for some subjects. Therefore, three different approaches were utilized to compare the between-treatment effects on the vitamin D_3 pharmacokinetic parameters.

Results: Efficacy outcomes have been reviewed in depth by Dr. Lau, please see his review for details. Efficacy findings are discussed briefly. This review concentrates on the safety findings of study P226.

Patient Disposition: A total of 244 healthy subjects were enrolled in the study (214 subjects in Part I and 30 subjects in Part II), of whom 9 discontinued. One subject discontinued due to an adverse event in Part I of the study. Two subjects were lost to follow-up after completing Part I, Period 1 only. These 2 subjects were replaced. One subject completed Part I Periods 1 and 2, but was lost to follow-up and discontinued at poststudy. A total of 207 subjects completed Part I, Periods 1 and 2 and were included in the pharmacokinetic analysis. In Part II a total of 28 subjects completed Periods 1 and 2 and were included in the pharmacokinetic analysis.

Study P226: Disposition

	Part I	Part II	Total
N	214 (%)	30 (%)	244 (%)
Completed	207	27	234
Withdrawals	7	3	10
Due to adverse events	1	0	1
Withdrew consent	4*	2*	6
Lost to follow-up	2*	1**	3

* subjects were replaced
**lost to follow-up post-study

Protocol Violations: There were no major protocol deviations or critical good clinical practice (GCP) deficiencies noted during Part I of the study. A protocol violation was noted in Part II of the study. On Day 6 of Period 1, 2 subjects received a vitamin D-enriched breakfast at ~6:30 AM. Both subjects consumed approximately 45 IU of vitamin D during this meal. The 120-hour postdose (final) blood sample for the vitamin D_3 assay was obtained ~2 hours after the meal. After inspection of the vitamin D_3 serum concentration curves for these subjects, it does not appear that the intake of the meal containing vitamin D influenced the serum concentration

curves. This is likely because of the lag observed following vitamin D_3 administration before intake is reflected in plasma levels. Therefore, the results from these subjects were included in the analysis.

Demographics: As outlined in the table below, the average age of the study population was 40.8 years. Fifty five percent were women and 45% were men. The majority (74%) of subjects enrolled in Part I of the study were Hispanic. In Part II of the study, 100% of subjects were Caucasian.

Study P226: Demographics			
	Part I	**Part II**	**Total**
N	214 (%)	30 (%)	244 (%)
Age (yrs.)	41.6 ± 11.8	35.2 ± 10.4	40.8 ± 11.8
Gender			
Female	119 (56)	14 (47)	133 (55)
Male	95 (44)	16 (53)	111 (45)
Race			
Caucasian	34 (16)	30 (100)	64 (26)
Black	20 (9)	0	20 (8)
Oriental	1 (<1)	0	1 (<1)
Hispanic	159 (74)	0	159 (65)
Weight (kg)	72.8 ± 11.6	71.2 ± 13.2	72.6 ± 11.8
Height (cm)	167.1 ± 9.0	170.4 ± 9.8	167.5 ± 9.2

Concomitant Medications: All subjects were instructed to refrain from taking any form of medication for a period starting 2 weeks prior to and continuing through the end of the study period. A total of 13 subjects in Part I and one subject in part II of the study received concomitant medications during the study as treatment for adverse events. Acetaminophen was the most common concomitant medication accounting for 11 of the 13 subjects in Part I and the one subject in Part II.

Pharmacokinetics: Pharmacokinetic parameters have been reviewed by Dr. Lau, please see his review for further details.

Alendronate: As outlined in the table below, after a single dose of study drug, the LS means for total urinary excretion of alendronate were 197.5 µg for the alendronate/D_3 combination tablet and 191.9 µg for the alendronate alone tablet. The GMR (90% CI) for the total urinary excretion of alendronate (alendronate/D_3 combination versus alendronate alone) was 1.03 (0.91, 1.17). The 90% CI fell within the pre-specified bioequivalence bounds of (0.80, 1.25).

Study P226: Total Urinary Alendronate Excretion After Single Dose		
	Aln + D combo	**Aln alone**
N	207	207
LS Mean ± SD	197.5 ± 329.1	191.9 ± 522.2
GMR	1.03	
95% CI	0.91 , 1.17	

Vitamin D: Since the pre-specified analysis method in the protocol generated non-physiologic negative $AUC_{0\text{-}120\ hr}$ for some subjects, the unadjusted data was analyzed as well as the following 2 alternate post hoc analyses: ANCOVA with concentration at time 0 hour as a covariate and model-fitted which adjusted for baseline vitamin D_3 serum concentrations. As outlined in the table below, the results of all 3 analyses are comparable. The LS means for vitamin D_3 $AUC_{0\text{-}120\ hr}$ (unadjusted for endogenous vitamin D_3 serum concentrations) were 296.4 ng·h/mL and 337.9 ng·h/mL for the alendronate/ D_3 combination tablet and 2800IU vitamin D_3 tablet, respectively. The $AUC_{0\text{-}120\ hr}$ GMR (alendronate/D_3 combination tablet versus vitamin D3 alone tablet) was 0.88 (90% CI 0.81, 0.95). The 90% CI fell within the pre-specified bioequivalence bounds of (0.80, 1.25).

Study P226: Vitamin D Pharmacokinetics		
	Aln + D combo	**Vit D alone**
N	28	28
Unadjusted		
AUC		
LS Mean ± SD	296.4 ± 375.5	309.8 ± 344.2
GMR	0.88	
95% CI	0.81 , 0.95	
Cmax		
LS Mean ± SD	5.9 ± 3.3	6.6 ± 3.1
GMR	0.89	
95% CI	0.84 , 0.95	
ANCOVA		
AUC		
LS Mean ± SD	297.5 ± 376.8	336.7 ± 343.0
GMR	0.88	
95% CI	0.82 , 0.92	
Cmax		
LS Mean ± SD	5.9 ± 3.3	6.6 ± 3.1
GMR	0.90	
95% CI	0.85 , 0.95	
Model Based Baseline Adjusted		
AUC		
LS Mean ± SD	143.1 ± 47.7	169.1 ± 37.3
GMR	0.85	
95% CI	0.76 , 0.94	
Cmax		
LS Mean ± SD	4.0 ± 1.1	4.6 ± 0.9
GMR	0.88	
95% CI	0.83 , 0.93	

Safety

Adverse Events Rates: All 244 subjects were included in the safety population. As outlined in the table below, a total of 85 [52 (21.8%) in the alendronate/ D_3 combination tablet group, 37 (17.5%) in the alendronate only group and 8 (26.7%) in the vitamin D only group] subjects reported adverse events. There were no deaths or serious adverse events. One subject in the alendronate only group withdrew from the study.

Study P226: Adverse Event Rates (Safety)			
	Aln+VitD	**Aln only**	**Vit D only**
N	238 (%)	211 (%)	30 (%)
One or more adverse event	52 (21.8)	37 (17.5)	8 (26.7)
Deaths	0	0	0
Serious adverse events	0	0	0
Withdrawal due to adverse event	0	1 (0.5)	0

Exposure: All subjects received the study medication assigned.

Deaths: No deaths were reported in this study.

Serious Adverse Events: There were no serious adverse events reported in this study.

Adverse Events Leading to Withdrawal: One subject withdrew from the study due to a clinical adverse event during Part I, Period 1 of the study. A 25 year-old male experienced severe shoulder and chest pain on Day 15 of the study and was discontinued from the study.

Adverse Events: As outlined in the table below, a total of 153 adverse events occurred in 85 subjects. The most common adverse event was headache, occurring in 20 subjects while receiving alendronate only, 33 subjects receiving the alendronate/ D_3 combination tablet and 4 subjects receiving vitamin D only.

	Part 1		**Part 2**	
	Aln+D	**Aln**	**Aln+D**	**D**
N, safety population	214 (%)	214 (%)	30 (%)	30 (%)
Subjects Reporting AEs	42	39	16	12
Events	67	58	24	13
Body as a whole	8	3	0	0
Gastrointestinal	24	28	5	3
Injury*	0	0	4	1
Nervous	32	22	7	4
Respiratory	0	1	3	0
Musculoskeletal	2	2	0	1
Reproductive	0	0	3	1
Vascular Disorders	0	1	0	0
Vision Disorders	1	0	0	1
Investigations	0	1	2	2

Adverse Events of Special Interest:

Fracture: There were no fractures experienced during this trial with this low risk population.

GI Adverse Events: A total number of 39 subjects (34 in Part I and 5 in Part II) reported gastrointestinal adverse events that could possibly be attributed to alendronate, as outlined in the table below.

Study P226: GI Adverse Event Rates (Safety)				
	Part 1		**Part 2**	
	Aln+D	**Aln**	**Aln+D**	**D**
N, safety population	214 (%)	214 (%)	30 (%)	30 (%)
Subjects Reporting AEs	17	17	3	2
Abdominal pain/discomfort	3	4	0	0
Diarrhea	8	8	2	1
Dyspepsia/ GERD	3	4	0	0
Nausea	3	4	1	1
Vomiting	6	3	0	0

Musculoskeletal Adverse Events: A total of 5 (4 in Part I and 1 in Part II) subjects reported musculoskeletal adverse events. There were no reports of bone pain.

Ocular Adverse Events: Two subjects reported eye adverse events. One subject, receiving the alendronate/D_3 combination tablet, reported mild keratoconjunctivitis sicca. One subject, receiving the vitamin D only tablet, reported mild conjunctivitis.

Laboratory: Two subjects had adverse events related to laboratory parameters. A 48 year old woman, with a baseline hemoglobin of 12.3 g/dL (normal 12-16 g/dL), was noted to have a decreased hemoglobin of 10.7 g/dL at poststudy, 17 days after taking the 2800IU vitamin D_3 dose. A 40 year old man, with a baseline hemoglobin of 15.9 g/dL (normal 14-18 g/dL) was noted to have a decreased hemoglobin of 13.7 g/dL at poststudy, 14 days after taking the 2800IU vitamin D_3.

Vital Signs: There were no clinically significant changes or trends in vital signs, physical examinations, or ECGs.

Discussion and Conclusions:

The geometric mean ratio for the 36-hour cumulative alendronate urinary excretion of the 70mg alendronate/2800IU vitamin D_3 combination tablet to the 70mg alendronate alone tablet was 1.03 and the 90% CI was (0.91 – 1.17). Based on the cumulative alendronate urinary excretion, the alendronate in 70mg alendronate combination tablet is equally bioavailable to the 70mg alendronate alone tablet. Bioequivalence could not be adequately assessed because the urine sampling intervals were not short enough to determine the maximum alendronate excretion rate.

The geometric mean ratio for the vitamin D_3 $AUC_{0\text{-}12h}$ (endogenous vitamin D_3 unadjusted) for the 70mg alendronate/2800IU vitamin D_3 combination tablet to the 2800IU vitamin D_3 alone tablet was 0.88 and the 90% CI was (0.81 – 0.95). The geometric mean ratio for the vitamin D_3 C_{max} (endogenous vitamin D_3 unadjusted) for the 70mg alendronate/2800IU vitamin D_3 combination tablet to the 2800IU vitamin D_3 alone tablet was 0.89 and the 90% CI was (0.84 – 0.95). Based on these observations, the vitamin D_3 bioavailability for the 70mg alendronate/2800IU vitamin D_3 combination tablet is similar to that for the vitamin D_3 alone tablet.

The adverse event profile of alendronate 70mg/vitamin D_3 2800IU was similar to the profile of alendronate 70mg.

10.2 Predefined Limits of Change for Laboratory Abnormalities

Study P227: Laboratory Abnormalities Predefined Limits of Change	
Laboratory Test	**Predefined Limits**
25-OH Vitamin D level	Value < 9
Serum Calcium (mg/dL)	Value < 8
	Value < 8.5
	Value > 10.5
Urine Calcium (mg/24hr)	Increase ≥ 25%
	Value > 300mg/24hr
Serum Phosphate (mg/dL)	Value < 2.0
	Decrease ≥ 30% and value < 1xLLN (2.50)
	Increase ≥ 30% and value > 1xULN (4.50)
Sodium (meq/L)	Decrease ≥ 10 and value < 1xLLN (133)
	Increase ≥ 10 and value > 1xULN (145)
Potassium (meq/L)	Increase ≥ 0.5 and value > 1xULN (5.00)
Blood Urea Nitrogen (	Increase ≥ 50%
Creatinine (mg/dL)	
AST, SGOT (IU/L)	Increase ≥ 50% and value > 1xULN (25.00)
ALT, SGPT (IU/L)	Increase ≥ 50% and value > 1xULN (25.00)
Alkaline Phosphatase (IU/L)	Increase ≥ 50% and value > 1xULN (90.00)
WBC (103/μL)	Decrease ≤ 20% and value < 1xLLN (4.80)
	Value < 1xLLN (4.80)
	Increase ≥ 20% and value > 1xULN (10.80)
Hematocrit (%)	Decrease ≤ 20% and value < 1xLLN (42)
Hemoglobin (gm/dL)	Decrease ≤ 20% and value < 1xLLN (14.0)
Platelets (103/μL)	Decrease ≤ 25% and value < 1xLLN (150)

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