MEDICAL REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: 20560-038 **Application Type:** sNDA

Sponsor: Merck **Proprietary Name:** Fosamax (alendronate sodium)

USAN Name:

Pharmaceutical Category: bisphosphonate **Route of Administration:** tablets, oral

Indication: (b) (4) **Dosage:** 5mg, 10mg

Reviewer: Bruce S. Schneider, MD **Dates of Review:** Feb.1, 2003-June 30, 2003

Chemistry Review: NA
Pharmacology Review: NA
Biopharmaceutics Review: J. Lau, PhD
Statistics Review: T. Sahlroot, PhD

REVIEW SUMMARY: Please see Executive Summary

OUTSTANDING ISSUES: None

(b) (4)

SIGNATURES:

Medical Reviewer: __Bruce S. Schneider, MD
_____ **Date:** June 30, 2003

Medical Team Leader: **Date:** _____

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Executive Summary

A. Recommendations

(b) (4)

Recommendation of Phase 4 Studies and Risk Management Steps: none

B. Summary of Clinical Findings

In response to a Written Request, Merck has submitted 12-month safety and efficacy data from an ongoing study of the use of alendronate in children with osteogenesis imperfecta (OI). The study was a randomized, placebo-controlled, multicenter trial that enrolled 139 patients with OI, aged 4-18 years. The patients were randomized 1:3 to receive placebo or alendronate (5 mg or 10 mg, depending on body weight) as double-blind therapy for up to two years, followed by an open-label extension.

Alendronate, 5 mg or 10 mg, produced a substantial increase in lumbar spine BMD (increase of 1 BMD z-score unit, equivalent to a placebo-subtracted increase of 26% in one year). The sponsor obtained hip BMD data on only six

patients; consequently, we have no indication of the efficacy of alendronate on peripheral skeletal sites in this population. An analysis of the key secondary efficacy endpoints, radiologically-confirmed and investigator-reported long-bone fractures, found no treatment-group differences. Alendronate treatment was associated with significant suppression of bone turnover markers, consistent with the known pharmacodynamic actions of the drug. There were no other treatment-related benefits of the drug, relative to placebo.

The safety and tolerability profile of alendronate in this population were acceptable, with few serious adverse events (only three of which were possibly related to alendronate) and no deaths. Children treated with alendronate had standing and sitting growth velocities that were essentially equal to those of patients treated with placebo.

C. Current therapeutic options for treating Osteogenesis Imperfecta: There is no approved medical treatment for OI in the United States. Treatment has focused on fracture management and surgical correction of deformities. There are published studies on the utility of various agents, including fluoride, calcitonin, anabolic steroids, growth hormone, and pamidronate, but there are no data from rigorous placebo-controlled trials. Allogeneic bone marrow transplantation has also been tried in a few children with Type III OI, which is the most severe non-lethal form.

D. Brief overview of clinical program

This study was performed in response to a Written Request for the study of the safety and efficacy of alendronate in the treatment of children with OI. There is reason to believe that a bisphosphonate might be beneficial in this population, based on the high bone turnover rates and low bone mineral density that accompany the disease. In addition, there have been a few uncontrolled studies that indicated that anti-resorptive therapy might be helpful.

The submission consists of 12-month safety and efficacy data from an ongoing study of the use of alendronate in children with osteogenesis imperfecta. The study was a randomized, placebo-controlled, multicenter trial that enrolled 139 patients with OI, aged 4-18 years. This is the first placebo-controlled study of the use of a bisphosphonate in patients with this disease. The patients were randomized 1:3 to receive placebo (PBO) or alendronate (ALN, 5 mg or 10 mg, depending on body weight) as double-blind therapy for up to two years, followed by an open-label extension. The primary efficacy outcome was change in BMD z-score from baseline to Month 12 of double-blind therapy. Key secondary outcomes were the proportions of patients with one or more radiologically-confirmed fractures and with one or more investigator-reported fractures (not necessarily confirmed radiologically). Based on an evaluation of the DSMB, the study had achieved its primary objective (lumbar spine BMD) and there were no other concerns that would preclude the continuation of the double-blind portion of the study for the second year. Accordingly, the results of data up to Month 12 were submitted in fulfillment of the Written Request. In addition, available safety and efficacy data up to Month 24 were submitted.

E. Efficacy

The study enrolled 139 patients with OI, aged 4-18 years. There were 78 boys and 61 girls. Seventy patients were < 12 years of age and 69 were > 12 years. The patients were roughly equally distributed among the three requested disease phenotypes (Type III, Type IV, and Type I OI associated with chronic pain and/or > three fractures/year for the two years prior to the study, or with limb deformity requiring surgery).

A total of 112 patients (86 ALN and 26 PBO) were included in the modified intention-to-treat analysis that carried forward the last observed data (MITT-LOCF). Ninety-seven of these patients had data within the Month 12 range, and 15 had Month 6 data carried forward.

The primary efficacy endpoint was clearly met. At baseline, both groups had very low lumbar spine BMD z-scores (the z-scores were -4.6 in both treatment groups). There was a substantial increase in lumbar spine BMD associated with alendronate, 5 mg or 10 mg. The increase in ALN was 1 BMD z-score unit; this was equivalent to a placebo-subtracted increase of 26% in one year. Similar increases in lumbar spine bone mineral density were noted, whether the data were expressed as BMD (in gm/ cm^2) or as bone mineral content (BMC). A responder analysis showed that a greater proportion of patients in ALN had increases of BMD that exceeded pre-specified thresholds, compared to PBO. Subgroup analyses showed that there was no group (weight, age, gender, race, pubertal status) in which the drug was not effective in increasing BMD. Increases in vertebral bone area and metacarpal cortical width were also seen in both treatment groups over the 12 months of double-blind therapy, but there were no significant between-group differences in these parameters. The sponsor obtained hip BMD data on only six patients; consequently, we have no indication of the efficacy of alendronate on peripheral skeletal sites in this population.

Alendronate treatment was associated with significant suppression of bone turnover markers, consistent with the known pharmacodynamic actions of the drug.

Despite these effects on bone turnover and BMD, an analysis of the key secondary efficacy endpoints, radiologically-confirmed and investigator-reported long-bone fractures, found no statistically significant or consistent treatment-related differences in fracture occurrence. About half the patients in each group suffered at least one fracture in the first 12 months, and the average number of fractures/patient was 1.1 in both groups.

Of interest, there was a trend in favor of alendronate in cumulative incidence of fractures and in proportions of patients with at least one investigator-reported fracture over the 12-month period (see Kaplan-Meier analysis in this review). Although the time to first fracture was numerically longer in ALN, compared to PBO, the difference between the groups was not significant. It will be important to

analyze data following 24 months of double-blind treatment to see if this treatment difference holds up.

There were no other treatment-related benefits of the drug, relative to placebo. This includes an analysis of bone pain, bone pain frequency, and pediatric disability scores.

F. Safety

Safety data up to month 12 and data up to Month 24 were submitted. Safety data were recorded on all 139 randomized patients. Of the 139 patients, 89 (81.7%) of ALN and 29 (96.7%) of PBO took at least 12 months of study medication (within pre-defined relative day range). The mean total duration of exposure in ALN was 317.7 days (range, 40 to 444 days) and, in PBO, 348.5 days (range, 270 to 378 days). The median exposure time was the same in both groups (356 days).

The study is ongoing, and, at the time of the submission 49 patients had received alendronate for up to two years. The sponsor included safety data past 12 months, and all safety data were analyzed in this review. For all safety data past 12 months (i.e., “Results up to 24 Months”), the median exposure times were 545 days in ALN (range 40-751) and 612 days in PBO (range 295-732).

Based on data submitted, the overall safety and tolerability of alendronate in the pediatric population with OI were favorable. The adverse event profile of alendronate was comparable to that of placebo, both in data up to 12 and up to 24 months. Six patients in the entire study population experienced at least one serious AE (excluding fractures) during the 12-month double-blind treatment period: Four in ALN (3.7%) and two in PBO (6.7%). Four more patients in ALN had a serious clinical adverse event after Month 12. In the opinion of the investigators, none of the serious AEs was related to study drug. However, I have reviewed the clinical reports and have concluded that it is possible that vomiting (leading to clinically serious dehydration) in two patients was related to alendronate. In addition, one case of leukopenia was reported in a patient taking alendronate. This is not known to occur with excessive frequency in adults treated with alendronate, but should be followed as a safety signal in children whether or not the drug is approved for this indication. No patient was withdrawn from therapy due to a serious AE.

Patients treated with alendronate had growth velocities (standing and sitting) that were at least as high as those of patients treated with placebo for the first twelve months; data available up to 24 months also showed no treatment-group differences in height velocities. The growth rates in pediatric patients with OI are less than in normal children, and there is substantial variability in growth measurements in affected individuals. Accordingly, a complete dataset up to Month 24 will help confirm the stability of this safety outcome.

A separate upper GI safety analysis was performed, and there was no indication that alendronate is associated with an increase in GI toxicity in this population, on the basis of the submitted data. However, I have raised the possibility that

alendronate contributed to the vomiting that was associated with dehydration in two patients.

Histomorphometry data derived from iliac crest biopsies were scheduled for all patients at baseline and at Month 24. To date, results are available on only 10 patients (7ALN and 3 PBO). Although two ALN patients had a prolonged mineralization lag time, there was no associated increase in osteoid thickness, which would be indicative of osteomalacia. Review of the complete histomorphometry dataset will be required before a full bone safety assessment is possible.

The sponsor addressed the potential problem of non-union or mal-union of fractures in OI patients treated with alendronate. This was not an overt clinical problem during the trial. However, it was not possible to conduct a formal comparison of the frequency of bone healing abnormalities between the two treatment groups, since not all patients had fractures at baseline and the total number of fractures present at baseline has not been evaluated. Thus we do not know whether alendronate may worsen the delay in fracture remodeling that is found in patients with OI. Further data are required to make this determination.

There were no deaths during the study (either in the first 12-month period or in the data reported for the 24-month period).

G. Dosing

The study employed two doses, 5 mg and 10 mg daily, based on body weight strata. (b) (4)

H. Special populations

(b) (4)

Clinical Review[1]

[1] Several tables and figures are taken directly from the sponsor's submission. Reviewer's tables are also indicated as such. Reviewer's Comments appear in **bold** text.

I. Introduction and Background

Osteogenesis imperfecta (OI) is an inherited disorder that is characterized by a generalized decrease in bone mass and bone strength. The disorder results from any of a number of mutations in the genes encoding the α1 or α2 chain of type I collagen. The mutations lead to underproduction of type I collagen and/or production of abnormal collagen fibrils. Other associated phenotypic abnormalities in some types of OI include blue sclerae, dental abnormalities, and hearing loss. The disease occurs in several forms, depending on the genotype. The most severe forms cause death in utero or soon after birth. The course of the milder forms is variable. There is an increased tendency to suffer multiple fractures, but the age at which fractures tend to occur varies among patients. Women are particularly vulnerable to fracture during pregnancy and after menopause.

Over 300 distinct mutations in the two genes that encode type I procollagen have been described in patients with OI. Many patients with type 1 OI have proα1 gene mutations that decrease levels of proα1 mRNA and decrease the rates of synthesis of proα1 peptide. In the more severe forms (types 2, 3, and 4), other mutations cause synthesis of abnormal peptide chains, leading to more severe phenotypic defects. For example, mutations that cause substitution of a bulky amino acid residue in place of glycine (glycine, the smallest of the amino acids, occupies every third position in the type I collagen molecule and is important for proper “stacking” of the collagen fibril) in one chain can interfere with proper folding of two otherwise normal procollagen molecules into a normal triple helix. In addition, there is often increased degradation of the imperfectly formed fibrils. Thus a mutation in one allele can function as a dominant negative.

Although it was originally thought that many of the identified mutations were neutral variations in DNA sequence, abundant data support the causal relationship between most of the mutations and the disease phenotype. These data are based on DNA linkage studies in affected families, the failure to identify lethal mutations in probands with corresponding sequences in unaffected parents, *in vitro* studies with cultured fibroblasts from affected patients, experiments with mice bearing mutated transgenes, and other lines of evidence. Most of the mutations have been found to be specific to families: unrelated patients rarely demonstrate the same mutations, even when the phenotypes are similar. This is not surprising, based on the molecular pathophysiology of OI.

Type I collagen is a major source of bone strength, and the integrity of bone structure is weakened by any mutation that reduces the amount of normal type I collagen fibrils. Of particular relevance, normal type I collagen is necessary for proper mineralization of bone matrix. Bone histomorphometric studies in patients with OI have generally provided evidence for increased bone resorption with reduced new bone formation. Rauch et al (*Bone* 26(6): 581-9, 2000) provided evidence for defects in all three mechanisms that normally increase bone mass in growing children: modeling of external bone geometry and growth, production

of secondary trabeculae by endochondral ossification, and thickening of these trabeculae by remodeling.

I have outlined the major features of the 4 classes of OI in the following table:

TYPE	BONE FRAGILITY	OTHER FEATURES	INHERITANCE
1	Mild-moderate, with osteoporosis, fractures	Blue sclerae; abnormal dentition in some	AD
2	Extreme; lethal course	Blue sclerae; abnormal dentition in some	Sporadic new mutations; germ line mosaicism
3	Severe osteopenia at birth; progresses with age, with multiple fractures; deformity and fracture of long bones and vertebrae	Blue sclerae in some; high incidence of hearing loss; abnormal dentition in some	AR or AD
4	Osteopenia with variable numbers of fractures and deformities;	Abnormal dentition in some; high incidence ;of hearing loss;	AD

	moderate to severe growth retardation	white sclerae	

The incidence of type 1 OI is about 1 in 30,000. Type 2 has an incidence of about 1/60,000 births but may be as high as 1/20,000. Types 3 and 4 may also have incidences as high as 1/20,000.

There is no specific therapy for any form of OI. Treatment has concentrated on management of fractures, surgical correction of deformities, orthotics, physical therapy, counseling, and other supportive measures. Aside from bisphosphonates, several agents have been used in an attempt to increase bone mass and prevent fragility fractures (calcitonin, fluoride, anabolic steroids), but none has proven effective. In a small study, increased spine BMD was noted in seven patients who received recombinant growth hormone for one year, relative to seven controls. Allogeneic bone marrow transplantation has also been tried in a few children with Type III OI.

Based on both theoretical considerations and a few published reports, there is reason to believe that bisphosphonate therapy may be of some benefit in treating OI. This would be particularly true of a bisphosphonate that targets osteoclasts and affects bone formation only secondarily. All forms of OI are marked by low bone mineral density. Histomorphometric studies have provided some evidence for increased rates of bone turnover in OI, and bisphosphonates are known to be effective in reducing bone turnover. If bisphosphonates are capable of increasing bone mass in OI, then it is possible that fracture rates would be reduced.

A review of the published literature supports the hypothesis that bisphosphonate treatment might be effective. Most of the studies have been small, open-label, and of limited duration. In the largest study (Glorieux et al, *NEJM* 339 (14): 947-52, 1998), which was uncontrolled, 30 children with severe OI, aged 3-16 years, were given i.v. pamidronate for periods from 1.3-5 years (every 4-6 months). The investigators noted a substantial increase in lumber spine BMD (42%), associated with a significant reduction in incidence of vertical fractures. The annualized BMD increase was about 42%, with a 27% increase in metacarpal cortical width. The average z-score improved from –5.3 to –3.4. There was an increase in the size of vertebral bodies, suggesting new bone growth. In another study of 9 children under age 3 (Plotkin et al, *JCEM* 85: 1846-50, 2000), treatment with i.v. pamidronate for 1 year reduced bone pain and increased BMD as early as 6 weeks following onset of therapy. Histomorphometric studies of iliac crest biopsies from patients in these studies demonstrated increases in cortical width and cancellous bone volume, due to increased trabecular number (with no change in trabecular thickness). There was no evidence for a mineralization defect in any of the treated patients. Other publications have reported even smaller studies or isolated cases. However, the results of bisphosphonate treatment have largely been beneficial. There have been no notable safety issues in these reports.

Thus there is a need for larger, controlled studies of the safety and efficacy of bisphosphonate use in patients with OI.

Alendronate is a potent bisphosphonate that was approved in 1995 for the treatment of postmenopausal osteoporosis. Other current indications include Paget's disease, osteoporosis in men (with or without hypogonadism), and glucocorticoid-induced osteoporosis in adults. The drug is selectively concentrated in bone and inhibits osteoclastic bone resorption via mechanisms that have not been completely elucidated. Alendronate binds tightly to bone mineral hydroxyapatite; however, there are abundant data suggesting that alendronate also exerts intracellular actions on osteoclasts themselves and that the drug acts primarily to inhibit osteoclast function. Alendronate does not appear in inhibit bone mineralization directly, and there is no information to suggest that alendronate is directly toxic to osteoblasts. Abundant histomorphometric data have provided no indication that chronic therapy with alendronate causes osteomalacia in adult humans or experimental animal models. [2] Furthermore, there is no evidence that the drug interferes with bone growth or fracture healing in animals. The effects of alendronate on bone growth, remodeling, and fracture healing in the pediatric population are currently unknown.

By inhibiting bone resorption, alendronate reverses the loss of bone mineral that accompanies estrogen-deficient states, such as menopause, and in glucocorticoid-treated adults. Consequently, bone mineral density increases at several skeletal sites, particularly those areas that are rich in trabecular bone. The preferential effect of alendronate on trabecular bone is due to the relatively high mineral turnover in this type of bone after menopause and in high turnover states. Alendronate resides in bone for many years: the terminal elimination half-life is 10 years. This long bone residence time is of some concern in a pediatric population. The concerns relate both to long-term effects on growing bone and the possibility that the long residence time in the skeleton will permit pharmacologically significant quantities of alendronate to re-enter the circulation long after the patient has discontinued the drug. If a young woman becomes pregnant after stopping alendronate, the small amount of drug that is present in the circulation might harm the fetus. Although these considerations are still theoretical, we are in the process of developing appropriate cautionary language for inclusion in bisphosphonate labels.

In several large trials in postmenopausal osteoporosis, alendronate has consistently demonstrated efficacy, in terms of increases in BMD at the spine and other skeletal sites, such as the hip. In addition, significant fracture efficacy (particularly at the spine) has been demonstrated. The major toxicity associated with alendronate use is gastrointestinal. Adverse events have included

[2] The complete array of intracellular actions of bisphosphonates has not been determined. Furthermore, the intracellular actions differ among the bisphosphonates. Some, those that resemble PPi, may be incorporated into ATP analogs, whereas the nitrogen-containing bisphosphonates may interfere with the mevalonate pathway and post-translational protein prenylation. The latter may affect intracellular protein "trafficking" processes in which nascent proteins are directed to specific intracellular locations. Such actions may increase the rate of cellular apoptosis. Bisphosphonates may also affect the activities of enzymes that are involved in matrix resorption, as well as proton pump activities that are required for acidification of resorption cavities.

esophagitis, gastritis, esophageal ulcer, GI bleeding, and even perforation. It is believed that many of these episodes can be prevented by remaining in an upright position for at least 30 minutes after taking the drug.

There are currently no controlled safety data on alendronate in the pediatric population. Potential areas for concern include GI toxicity and long-term effects on bone growth and fracture healing. As indicated above, the bone safety concerns in children are largely theoretical; nonetheless, a comprehensive bone safety monitoring program should accompany any study of alendronate in children.

Published studies of the effects of alendronate in an infant mouse model (the *oim/oim* mouse[3]) have shown that alendronate reduced fracture risk, did not significantly delay radiological remodeling of the callus following controlled femoral fracture, and increased femoral BMD and diameter (Camacho et al, *Calcif. Tissue Int., 2001).* Negative effects included slightly shorter femora and persistence of calcified cartilage in metaphyses of alendronate-treated mice (presumably due to inhibition of osteoclast action). These changes could theoretically result in further growth retardation in children with OI who are treated with alendronate.

The limited clinical pediatric data that are available do not suggest that alendronate is deleterious to bone. Bone safety parameters that have been studied thus far include skeletal growth, fracture healing, radiological changes, histology, and dental development. None of the small studies of alendronate in OI have reported that the drug adversely affects any of these parameters. However, it should be noted that all the published studies have been small or of short duration and uncontrolled. These studies have generally demonstrated increases in BMD in association with alendronate treatment. Of relevance to the current protocol, a published bone histology study of 17 children with OI showed that cortical width increased by 57% during treatment, while cortical porosity decreased by 39%. All bone surface indicators of cancellous bone remodeling declined, and there was no evidence for a mineralization defect (Rauch et al, abstract in *J. Bone Mineral Res.* 1999)[4].

In summary, there are specific safety issues that should be addressed in any study of bisphosphonates in the pediatric population. However, based on extensive controlled and uncontrolled data, there is no indication that alendronate is harmful bone in adults or in children during very limited observations. The pre-clinical data also support the use of alendronate, although the two negative outcomes in the *oim/oim* mouse studies (described above) mandate scrutiny of

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[3] Mice homozygous for the *oim* mutation (*oim/oim*) are deficient in pro-α2 (I) collagen; consequently, the majority of their type I collagen is an α1 (I) homotrimer. The phenotype most closely resembles that of human type 3 OI.

[4] In the current application, the sponsor presents a full review of the safety and efficacy of alendronate and pamidronate use in pediatric patients with OI and glucocorticoid-induced osteoporosis. The review also covers the body of knowledge of bisphosphonate use in relevant pre-clinical models.

linear growth during clinical trials. There are sufficient preliminary data to suggest that bisphosphonate therapy may confer substantial benefit to children with OI. These considerations led the Agency to issue a Written Request for the study of alendronate in pediatric patients with severe, but non-lethal OI (types 3, 4, and 1 with evidence of significant clinical disease).

II. Clinically relevant findings from chemistry, toxicology, microbiology, biopharmaceutics, statistics, and other sources

Please see accompanying biopharmaceutics review by Dr. Lau. Merck performed a bioavailability study in response to the Written Request. The mean oral bioavailability of alendronate (95% CI) was 0.43% (0.28%, 0.64%), with respect to a 125 μg intravenous dose in OI pediatric patients weighing < 40 kg who received 35 mg orally. The mean oral bioavailability was 0.56% (0.36%, 0.87%) for OI pediatric patients weighing ≥ 40 kg who received 70 mg orally.

The oral bioavailability of alendronate in pediatric patients with OI is similar to that of adults (historical data).

III. Human pharmacokinetics and pharmacodynamics

Per masterfile. Please see accompanying biopharmaceutics review.

IV. Data sources and review methods

All data were derived from the Clinical Study Report of Merck's Protocol 135. Data were submitted in both paper and electronic forms.

V. Review of Protocol 135: *"A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Of Oral Alendronate Sodium in Pediatric Patients with Severe Osteogenesis Imperfecta, Followed By An Open-Label Extension."*

V.1 Regulatory history of the study:

The sponsor outlines the entire history of the study on pages 39-45 of the submission. I will describe only the most significant aspects of this history.

The original protocol for this study was written by representatives (b) (4) in 1998. The protocol was submitted to the FDA under a sponsor-investigator IND (b) (4) In October 2000, Merck contracted with (b) (4) to assume an active role in the conduct and management of the study, and in December 2001 the firm notified the FDA that regulatory sponsorship was

being transferred to Merck's IND # (b) (4) Shortly thereafter, the (b) (4) original IND (b) (4) was inactivated at the investigator's request.

On May 31, 2000, Merck proposed that the Agency issue a Written Request for the study of OI in children. Although the Division originally asked for fracture incidence as a primary endpoint, agreement on BMD as the primary endpoint was reached. This agreement followed consideration of the reliability of measurement and the predicted baseline fracture incidence. Accordingly, in the Written Request (issued in October 2000), BMD was the primary endpoint and fracture rate was secondary.

Details of amendments and Merck's arrangements for the establishment of a Protocol Steering Committee and Data Safety Monitoring Board are presented in the application and, with the exception of major amendments, will not be repeated here.

In June 2001, Merck submitted a protocol amendment (135-01) that revised the original (b) (4) protocol. The study was to be extended for at least one year (open-label) following each patient's double-blind period, in order to gather additional safety data Plans for interim analyses were presented in subsequent protocol amendments, along with modifications of the statistical DAP. Plans for reporting fractures were also discussed and submitted.

In August 2001 the DSMB reviewed the Interim Analysis results, which included fractures as well as other efficacy and safety data. The DSMB reported that there were no safety issues and recommended that all patients who had completed, or would complete, the full 24 months of double-blind study medication could be transferred to open-label alendronate. The DSMB noted several discrepancies in efficacy outcomes: between BMD and fracture data, between radiologically confirmed and investigator-reported fractures, and between radiologically confirmed fractures and vertebral size[5]. In their view, the radiologically confirmed fracture data may not have accurately reflected the true fracture rates in the two treatment groups. The Protocol Steering Committee (PSC) accepted the recommendations of the DSMB.

Further details regarding the ascertainment of fractures are provided in the submission.

A Safety Update Report, summarizing all clinical and laboratory AE data up to February 11, 2002, was reviewed by the DSMB, without comments or suggestions.

In April 2002, the DSMB reviewed the results of the radiology data for patients who were included in the Interim Analysis in 2001. The DSMB concluded that there was no reason to stop the study on the basis of safety concerns.

[5] Long bone x-rays were obtained at baseline and yearly thereafter. These were termed "radiologically confirmed fractures." In addition, fractures that were reported by investigators, whether or not confirmed radiologically, were termed "investigator-reported fractures."

In May 2002 Merck made administrative changes to the amended DAP to define "Day 365" for the purposes of assessing AEs and investigator-reported fractures.

In August 2002 the DSMB reviewed the results of the 12-month data for all study patients, received by the cutoff date of June 25, 2002. This analysis is the "Final Analysis" for the present submission. The DSMB was asked the following two questions regarding the data:

1) Have the primary hypotheses been met?
    a) There will be a greater improvement in mean lumbar spine BMD z-score at Month 12, relative to placebo.
    b) Alendronate will be well tolerated and have a generally favorable safety profile.

2) A total of 27 of the 139 patients originally enrolled are still receiving double-blind therapy. Should these patients be switched to open-label alendronate at their next study visit, even before they reach the Month 24 time point?

The DSMB determined that the primary study endpoint had been met. However, the DSMB thought that the remaining patients should continue double-blind for 24 months before switching to open-label therapy, in order to collect more data on fracture healing and growth.

The PSC agreed with the DSMB to continue the 27 patients on double-blind therapy until Month 24, in order to obtain data on BMD, fracture incidence, bone pain, histology, height, and other endpoints.

V.2 Design

Study 135 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial of the safety and efficacy of alendronate in treatment of pediatric patients with OI.

The two primary hypotheses were:

1. A greater improvement in mean lumbar spine BMD (L1 to L4) z-score (the number of standard deviations from the mean for age-matched healthy controls) will be seen at Month 12 with the doses of alendronate combined relative to placebo.

2. Alendronate will be well tolerated and have a generally favorable safety profile.

Objectives

The objectives of the study were:

"To compare the effects of 2 doses of alendronate combined versus placebo, in

pediatric patients ages 4 through 18 with severe osteogenesis imperfecta, for:

Primary
1. Change in mean lumbar spine (L1 to L4) BMD at Month 12.
2. Safety and tolerability.

Secondary
1. Radiologically confirmed fractures (those confirmed by a panel of central radiologists) and investigator-reported fractures (not necessarily confirmed radiologically).
2. Body mass index (BMI).
3. Cortical width at the midpoint of the second left metacarpal as measured from hand radiographs.
4. Cortical width as assessed by histomorphometric analysis of iliac crest bone biopsy samples.
5. Osteoid volume as assessed by histomorphometric analysis of iliac crest bone biopsy samples.

Exploratory
1. Functional capabilities and performance of daily functional activities in self-care and mobility as measured by the Pediatric Evaluation of Disability Inventory (PEDI) instrument, parental assessment of physical activity, and grip strength.
2. Vertebral height measurements.
3. Biochemical markers of bone turnover (NTx/creatinine, serum total alkaline phosphatase, and osteocalcin), and indices of calcium homeostasis (serum total alkaline phosphatase, and osteocalcin), and indices of calcium homeostasis (serum calcium, phosphate, parathyroid hormone, various metabolites of vitamin D, and urine calcium corrected for creatinine).
4. Bone pain."

This study is proceeding at the time of this review. The study is conducted at 16 Shriners Hospitals (15 in the US and one in Canada). The study protocol consists of an initial two-week, single-blind placebo period to test compliance with the dosing regimens. This is followed by a randomized, double-blind, parallel-group, placebo-controlled treatment period. In this period, patients are treated with study drug for a maximum of 24 months. The double-blind treatment period is followed by a one-year open-label extension.

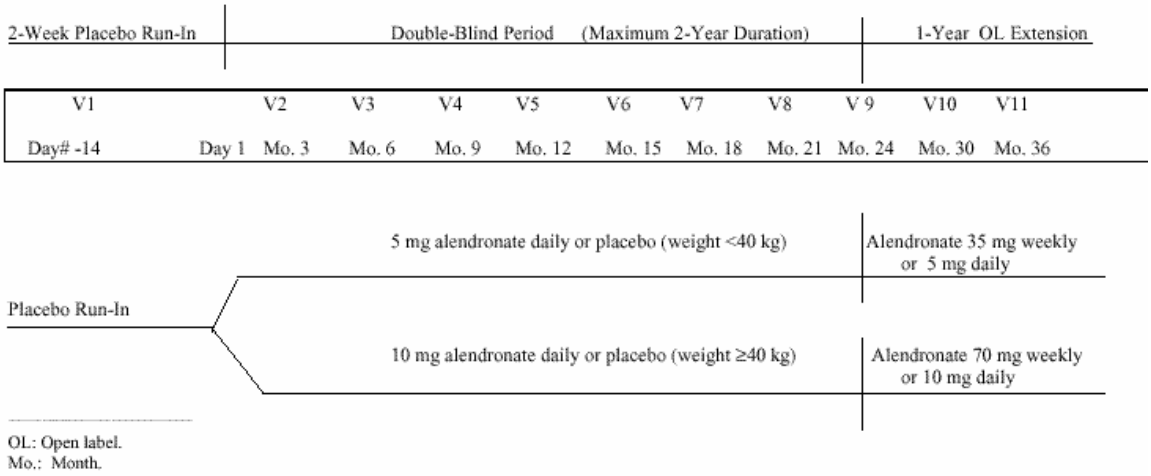
During the double-blind treatment period, patients receive oral alendronate (5-mg or 10-mg tablets daily, based on baseline body weight) or placebo tablets. During the open-label extension, all patients receive oral alendronate, 35-mg or 70-mg tablets on a once-weekly basis or 5-mg or 10-mg tablets daily.

Each patient will participate in the study for a maximum of three years[6].
The duration of the study itself (time from entry of first patient to conclusion of last patient) is five years.

Of note, in the study report, all references to specific time points (e.g. “Month 12”) do not indicate patient data collected at a specific calendar date in reference to the time frame of the study. Instead, day ranges relative to the start of double-blind treatment were established for all efficacy analyses. For the primary endpoint, “Month 12” was defined (in both the WR and the DAP) as Study Day 365 +/- 90 days. Furthermore, references to a period of observation (e.g., safety results up to Month 12) indicate events occurring up to and including that study time point. They do not indicate events occurring up to a specific calendar date. For example, in an adverse event summary, “Results up to Month 12” indicates all AEs that began on or before each patient’s study date 365 and is not a summary of AEs that began during the first calendar year after the initiation of the study.

A schematic of the study is provided by the sponsor in the following figure:

[6] The first patient started double-blind study medication on May 14,1999. The last patients started in April 2001 and are expected to complete their three-year study participation in April 2004.



V.3 Subjects

Subjects were required to meet the following inclusion/exclusion criteria:

Inclusion criteria:

1. The patient was a male or female 4 through 18 years at entry into the study.

2. The patient had osteogenesis imperfecta Type III or IV, or Type I with chronic pain and/or >3 fractures (including vertebrae) per year with minimal trauma for the previous 2 years, or with limb deformity requiring surgery.

3. The patient had to be able to stand or sit upright for at least 30 minutes following dosing and able to comply fully with all the dosing instructions.

Exclusion criteria:

1. Pregnancy at baseline or at any time during the study.

2. Patients regularly using drugs that alter gastric pH (i.e., H2 blockers and antacids) were excluded from participation in the study. However, calcium supplements were allowed if used to achieve an adequate daily calcium intake, provided that they were not taken within 30 minutes of a dose of study medication.

V.4 Discontinuation of patients from therapy

Patients could be discontinued from study therapy for any of the following reasons:

- occurrence of a clinical or laboratory adverse experience;
- loss of patient to follow-up;
- protocol noncompliance;
- voluntary withdrawal from the study.

Additional causes for discontinuation:

1. The patient took any bone-active medication, including any experimental or marketed bisphosphonate or calcitonin.
2. The patient experienced severe, uncontrolled pain of 3 months' duration. The pain must have interfered with activities of daily living and required analgesic medication.
3. Any medical condition or personal circumstance occurred that exposed the patient to substantial risk or precluded adherence to the requirements of the study.
4. Pregnancy.
5. The patient became incapable of standing or sitting upright for at least 30 minutes following dosing or was unable to comply fully with all dosing instructions throughout the study.

V.5 Protocol and treatments

Patients who entered the double-blind treatment protocol were stratified according to body weight. Patients weighing < 40 kg were randomized (3:1) to receive alendronate 5 mg daily or matching placebo. Patients whose body weight at screening was ≥ 40 kg were randomized (3:1) to receive alendronate 10 mg daily or matching placebo.

Determination of alendronate dose:

The sponsor determined the doses of alendronate on the basis of several factors, including available clinical data on the use of alendronate in adults and children, patient size (body weight), and previous experience with pamidronate, another bisphosphonate.

There is by now a vast experience with daily oral doses of alendronate (5 mg and 10 mg), and with weekly alendronate 35 and 70 mg, in the prevention and treatment of osteoporosis in postmenopausal women. In addition, there is a considerable efficacy and safety database for these alendronate doses in osteoporotic men and in adults with glucocorticoid-induced osteoporosis. However, there is only limited information on the use of alendronate in children with low bone mass. In small studies, alendronate doses of up to 10 mg daily have been used children with osteoporosis due to a variety of causes. These studies have generally demonstrated beneficial effects and a favorable safety profile. Based on this limited experience, the sponsor thought that alendronate 5

mg daily in children weighing <40 kg, or 10 mg daily in children weighing ≥ 40 kg, would have comparable safety and efficacy outcomes in children with OI.

The cutoff weight, 40 kg, approximates the 50th percentile for a 12-year-old boy or an 11.5-year-old girl. This weight has been used as a cutoff in other pediatric studies.

The average dose of intravenous pamidronate used in the open-label study of OI was approximately 6.8 mg/kg/year, corresponding to an average pamidronate dose of approximately 19 μg/kg/day for a 35-kg child. At the time the present study was started, there were no bioavailability data on oral alendronate in pediatric patients. Merck assumed that the oral bioavailability of alendronate in children would be similar to that in adults (approximately 0.65%). Based on earlier studies demonstrating that alendronate is at least 15 times more potent than pamidronate in vivo, Merck considered that a 5-mg alendronate dose given daily to a 30-kg child would be therapeutically equivalent to about 16 μg/kg/day of intravenous pamidronate[7].

Four years after the present clinical trial began, the sponsor concluded a bioavailability study that confirmed that the bioavailability of oral alendronate in children was essentially the same as in adults. This study, submitted as part of the present application and reviewed separately by Biopharmaceutics, employed a two-period, randomized, crossover study in which 24 children (aged four to 16 years) with OI Type I received alendronate 125 μg IV and oral alendronate, 35 or 70 mg (for patients whose body weight was < 40 kg or ≥ 40 kg, respectively), with doses separated by a two-week washout period. Urine was collected for 24 hours to determine the total urinary excretion of alendronate.

Twenty-four patients successfully completed the study. The bioavailability of oral alendronate was 0.43% (0.28, 0.64, 95% CI) in the children weighing <40 kg and 0.56% (0.36, 0.87) in the children weighing > 40 kg. These results were compared with historical data in adults. There was essentially no difference in this comparison between the geometric mean ratios of bioavailability of oral alendronate GMR [pediatric/adult]=0.74, 95% CI 0.51, 1.07), or in the total urinary excretion of alendronate following the IV dose (GMR=1.09, 95% CI 0.96, 1.23).

The sponsor concluded that the bioavailabilities of single oral doses of alendronate 35 mg (for children <40 kg) and 70 mg (for children >40 kg) were similar to each other and to results found in earlier studies in adults. In addition,

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[7] These estimates were based on the calculation that 0.65% of a 5-mg oral dose, divided by 30 kg and the multiplied by a factor of 15 (potency) would be therapeutically equivalent to 16-17 μg/kg/day of pamidronate. Similarly, a 10-mg dose given to a 50-kg child (thus 0.0065 x 10, divided by 50, and then multiplied by 15) was considered to be therapeutically equivalent to approximately 20 μg/kg/day of pamidronate. (b) (4)

the total urinary excretion of alendronate following the intravenous dose was the same for younger and older children. The urinary excretion of the drug following intravenous administration was no different from results found earlier in adults. Since alendronate distributes in bone or in urine, the data suggest that the percent distribution of the drug in bone remains roughly the same, independent of age.

Schedule of visits and procedures

A schedule of clinical observations and laboratory measurements for the 24-month double-blind period is presented in the following table.

	Prestudy	Treatment Months							
Visit Number:	1	2	3	4	5	6	7	8	9†
Study Month:	0	3	6	9	12	15	18	21	24
Sign consent form	X								
Clinic visit	X	X	X	X	X	X	X	X	X
OI history	X								
OI clinical evaluation (including height)	X	X	X	X	X	X	X	X	X
PEDI and grip strength‡	X		X		X		X		X
Biochemistry§	X	X	X	X	X	X	X	X	X
Radiology	X				X				X
Densitometry	X		X		X		X		X
Declomycin labeling/bone biopsy	X								X‖
Record fractures and adverse experiences	X¶	X	X	X	X	X	X	X	X
Dispense study medication	X#	X	X	X	X	X	X	X	X††
Telephone call to assess compliance	Required once-a-week for the first 4 weeks after a patient starts taking once-weekly open-label alendronate to assess compliance								

† If a patient discontinued during the double-blind period, ideally all procedures listed for the final double-blind visit (Visit 9) would have been completed. If the patient's previous dual-energy x-ray absorptiometry (DEXA) was performed within the prior 2 months, or if radiographs were conducted within the prior 6 months, those procedures did not have to be conducted at an Early Discontinuation Visit.

‡ The Pediatric Evaluation of Disability Inventory (PEDI) and the grip strength test were required at the "Switch" Visit in all patients. See Sections I.E.1. and I.E.4. in Protocol 135-03 for further details regarding other procedures required at the "Switch" Visit.

§ A complete blood count (CBC) was conducted locally at every visit, as well as a urine or serum pregnancy test in females of childbearing potential. In addition, a serum sample and a second morning void urine sample were collected at every visit and sent to the Montreal Shriners Hospital central laboratory for biochemical markers of bone turnover and calcium metabolism. A second morning void urine sample was also collected once a week for the first 3 months of the double-blind period. A serum sample was collected once from each patient during the study and sent to a central laboratory in Montreal for genetics (DNA) testing.

‖ All patients switched to open-label alendronate were required to have their second bone biopsy (if not already completed) at their Switch Visit, provided that both of the following conditions were met: (1) their baseline bone biopsy was adequate (evaluable), and (2) their Switch Visit was at Month 12 or later.

¶ All fractures were recorded on the Fracture Report Form.

During the baseline period one bottle of single-blind placebo medication (2-week supply) was dispensed.

†† A 6-month supply (2 bottles) of open-label alendronate was dispensed at the Month 24 visit according to the dosing guidelines in the protocol if the patient continued in the open-label extension.

OI = Osteogenesis Imperfecta.

A schedule of procedures for the open-label period is presented below:

	Extra Visit†	10	11‡
Study Month:		30	36
Clinic/hospital visit	X	X	X
OI clinical evaluation (including height)	X	X	X
PEDI§ and grip strength	X	X	X
Biochemistry‖	X	X	X
Radiology¶	X		X
Densitometry#	X		X
Record fractures and adverse experiences††	X	X	X
Dispense study medication‡‡	X	X	

† All patients who completed their Month 24 visit prior to being switched to open-label alendronate were required to return to the clinic for an "EXTRA VISIT" before beginning the open-label extension of the study. See Section I.E.1., Summary of Study Design, in Protocol 135-03 for further details regarding the "EXTRA VISIT."

‡ If a patient discontinued during the open-label extension, ideally all procedures listed for the final visit (Visit 11) would have been completed. If the patient's previous dual-energy x-ray absorptiometry (DEXA) was performed within the prior 2 months, or if radiographs were conducted during the prior 6 months, those procedures were not required at an Early Discontinuation Visit.

§ Pediatric Evaluation of Disability Inventory.

‖ At the "Extra Visit" (if it occurred >2 months following the Month 24 visit) and at Visits 10 and 11, a complete blood count (CBC) was conducted locally, as well as a urine or serum pregnancy test in females of childbearing potential (which is also required anytime pregnancy is suspected). In addition, a serum sample and a second morning void urine sample were collected at these same time points and sent to the central laboratory in Montreal for biochemical markers of bone turnover and calcium metabolism. See Section I.E.1., Summary of Study Design, in Protocol 135-03 for further details regarding the "EXTRA VISIT."

¶ Radiographs were not required at the "Extra Visit" if they were obtained within the prior 6 months.

Densitometry was not required at the "Extra Visit" if it was done within the prior 2 months.

†† All fractures occurring during the study were recorded on the Fracture Report Form.

‡‡ A 6-month supply (2 bottles) of open-label alendronate was dispensed and the dosing instructions carefully reviewed with the patient/parent.

OI = Osteogenesis Imperfecta.

Complete Blood Count Analyzed Locally†

Hemoglobin
Hematocrit
Total white blood cell count including differential
Platelet count
Red blood cell count
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Red cell distribution width (RDW)
Mean platelet volume (MPV)

Central Laboratory Serum Analyses‡

Calcium§
Phosphate‖
Creatinine§
Total alkaline phosphatase‖
Parathyroid hormone (iPTH)‖
Calcitriol ($1,25[OH]_2D_3$)§
Calcidiol ($25\text{-}OHD_3$)¶
$24,25(OH)_2D_3$¶
Osteocalcin#
Genetics test for OI collagen mutations††

† A complete blood count was conducted locally at every study visit.

‡ A serum sample was collected at every visit and sent to the Montreal Shriners Hospital central laboratory for biochemical markers of bone turnover and calcium metabolism.

§ Analyzed at baseline and Months 3, 6, 9, 12, 15, 18, 21, and 24.

‖ Analyzed at baseline and Months 3, 6, 9, 12, 18, and 24.

¶ Analyzed at baseline and Months 12 and 24.

Analyzed at baseline Months 6, 12, 18, and 24.

†† A serum sample for genetics testing for collagen mutations was collected once from all patients during the double-blind period of the study.

Urine analyses that were analyzed at the Central Laboratory are listed below.

Central Laboratory Urine Analyses[†]
Calcium corrected for creatinine (calcium/Cr)[‡]
N-telopeptides of Type I collagen (NTx)[‡]
Cyclic-adenosine monophosphate (c-AMP)[§]

[†] A second morning-void urine sample was collected and sent to the Montreal Shriners Hospital for analysis.
[‡] Collected once a week for the first 3 months of the double-blind period, and at Study Months 6, 9, 12, 15, 18, 21, and 24 and analyzed at those time points.
[§] c-AMP will be tested at baseline and Month 24 only. Therefore, no c-AMP results are presented in this report.

The specific analyses performed on the trans-iliac biopsies obtained for each patient at baseline and at Month 24 are listed below:

Analyses Conducted on Bone Biopsy Samples Obtained at Baseline and Month 24
Cancellous Bone
Bone volume/tissue volume (BV/TV)
Trabecular thickness (Tb.Th)
Osteoid volume/bone volume (OV/BV)
Osteoid surface/bone surface (OS/BS)
Osteoid thickness (O.Th.)
Mineralizing surface/bone surface (MS/BS)
Mineral apposition rate (MAR)
Eroded surface/bone surface (ES/BS)
Cortical Bone
Cortical width (Ct.Wi)

Documentation of treatment compliance

The investigators assessed treatment compliance by tablet count at each study visit. In addition, some of the patients kept diary cards, which were reviewed by the staff. Neither the original (b) (4) protocol, nor any of the protocol amendments mandated the use of diary cards.

V.6 Efficacy outcomes

The primary efficacy outcome measurement was lumbar spine (L1 to L4) BMD. The primary analytical response variable was change in L1-L4 BMD z-score from baseline to Month 12 in the alendronate group, as compared to the change in placebo. BMD was measured according to routine procedures using Hologic densitometers. (b) (4) served as the quality control center for the collection of all DEXA and x-ray data. (b) (4) provided all study sites with a DEXA Manual for the collection of DEXA data.

Measurements of femoral neck BMD and BMC were not determined in all patients because there are no reliable normative data for these anatomic sites in children and because it is difficult to position children with this disease with sufficient consistency to permit sequential femoral neck scans.

The sponsor also assessed the effects of alendronate on cortical bone by measuring cortical width at the midpoint of the second left metacarpal (measured, by a central radiologist, from radiographs of the left hand) and cortical width by iliac crest bone histomorphometry[8]. These measurements were secondary efficacy outcomes.

The other key secondary efficacy outcomes were the number of new radiologically confirmed (by a panel of central radiologists) long-bone fractures at Month 12 and the number of investigator-reported fractures up to Month 12 (these fractures were not necessarily confirmed radiologically). (b) (4) provided all sites with procedures for collection of x-rays for the study.

The sponsor also performed several exploratory measurements, including vertebral height and biochemical markers of bone turnover (urinary NTx/creatinine, serum total alkaline phosphatase, and osteocalcin).

Other exploratory efficacy measurements included functional capabilities and performance of daily activities in self-care and mobility (PEDI instrument, grip strength, bone pain, and parental assessment of physical activity).

Two of the histomorphometric parameters were intended to be exploratory efficacy measurements. These were bone volume/tissue volume, and trabecular thickness.

Details of the procedures for BMD determinations are provided in the application. The change from baseline in BMD z-score was the primary efficacy measurement. The sponsor also measured bone mineral content (BMC), and vertebral area BMD (areal BMD), for the purpose of confirming the primary results.

Comments: The use of BMD z-score as the primary BMD outcome variable (as compared with the % change in BMD from baseline, which is generally applied to studies in adults) is appropriate in the pediatric population, because BMD changes with growth of the child and increases substantially at puberty.

All BMD measurements were performed at Visit 1 (screening) and every 6 months thereafter during the first two years of the trial. BMD determinations

[8] In a previous open-label pamidronate study in children with OI, cortical width (at the midpoint of the second left metacarpal) increased by 27% per year.

(DEXA) were performed with Hologic densitometers (model QDR 1000, or 2000, or 4500).

For measurement of BMD in patients with very low-density vertebrae, the Radiology Department (b) (4) manually mapped all low-density vertebrae that the Hologic low-density software was unable to identify precisely. Using these measurements, which identified vertebral borders, lumbar spine BMD was then defined as total BMC/total area of the four LS vertebrae L1-L4. Lumbar spine BMD measurements were

accepted only if the BMC and area could be assessed for all four L1-L4 vertebrae.

Of note, the sponsor included in the analysis all L1 to L4 vertebral levels that could be measured by the Hologic densitometry software. This included vertebrae with a possible crush fracture, regardless of when the fracture occurred during the study.

Comments: This approach is unusual for BMD studies. Normally, patients or vertebral BMD data are excluded if there are crush fractures because the BMD might be artifactually increased in the affected vertebral body. This is due to reduction of vertebral bone area (by the fracture) with unchanged BMC. In this study, such cases were permitted entry into the study and the baseline and on-study BMD data (i.e., when there were incident vertebral fractures) were retained. The sponsor presents the following as justification for including vertebrae with crush fractures:

(1) the presence or absence of crush fractures in growing children and particularly in children with severe OI could be difficult to diagnose,
(2) crush fractures could improve in children (usually not the case in adults),
(3) z-scores could be calculated by the Hologic densitometry only when all 4 vertebral levels were measured, and
(4) crush fractures, and consequently artificially increased BMD values, were expected to occur more frequently in the placebo than in the alendronate group.

We have very little data on which to judge the merits of each of these arguments conclusively. Such data would have to be derived from careful, long-term radiological studies in children with OI, and this territory is still somewhat "uncharted." Certainly points 1 and 4 are reasonable. Point 2 is speculative. Point 3 relates to the ability to conduct the z-score analysis. Overall, the uncertainty in performing BMD studies may match the claimed uncertainty in using fracture as an endpoint. However, it is my opinion that including vertebrae with crush fractures will mot likely increase the "noise" in both arms of this randomized trial. I also agree with the sponsor that any artifactual increase in the observed BMD will occur more frequently in placebo than in the alendronate group. Overall, if the treatment group

differences in BMD are large, these considerations become less important. As it turned out, this was indeed the case.

This population has a high baseline fracture rate, often necessitating orthopedic procedures. Because metallic devices (e.g., rods, pins, screws) placed on vertebrae during the study could invalidate BMD measurements, the sponsor excluded data derived from vertebrae in which these objects were in the field of view of the densitometer.

For fracture counts, AP and lateral radiographs of the upper extremity long bones (humerus, radius, and ulna) were obtained at baseline and yearly thereafter. Similarly, lower extremity long-bone (femur, tibia, and fibula) x-rays were obtained at baseline and yearly thereafter.

For vertebral heights and shapes, thoracic/lumbar spine lateral radiographs were obtained at baseline and yearly thereafter.

For bone age and cortical width assessments left hand and wrist PA radiographs were obtained at baseline and yearly thereafter. For bone age determination, the sponsor used the Gruelich-Pyle grading scale. The width of the second left metacarpal bone was used as a measure of cortical width.

The sponsor obtained iliac crest bone biopsy specimens at baseline and Month 24 for histomorphometric analyses (see list of nine parameters in **V.5** above) and for measurement of cortical width.

All fractures were recorded by the central radiologist, who also described the morphometry of the T4 to T12 and L1 to L5 vertebrae. The central radiologist did not document the presence of spinal fractures because there are no established criteria for assessing these fractures in children. Instead, the radiologist recorded T4 through T12 and L1 through L5 anterior, midline, and posterior vertebral body heights.

Investigator-reported fractures: As described above, these fractures were not necessarily confirmed radiologically. They were recorded at each study visit by the investigator, who interviewed the patient (parent/legal guardian).

Biochemical markers of bone turnover and indicators of mineral metabolism: Urine and serum samples were collected at every study visit and sent to the central laboratory (b) (4) The serum sample was analyzed for levels of calcium, phosphate, creatinine, total alkaline phosphatase, iPTH, vitamin D metabolites (25-OH D3, 1,25(OH)2D3, and 24,25(OH)2D3), and osteocalcin. The urine samples (which were also obtained once-weekly for the first three months of the study) were analyzed for: calcium/Cr, NTx, and c-AMP.

Finally, for each patient, serum was obtained for determination of collagen gene mutations.

Other efficacy outcomes: During the double-blind phase of the study, the Pediatric Evaluation of Disability Inventory (PEDI) was conducted every six months by an occupational therapist. The following domains were included: self-care, mobility, and social function.

Grip strength was measured in both hands using a hand dynamometer every 6 months during the double-blind phase of the study.

History of bone-pain frequency, including use of analgesics, was assessed at each study visit from patient diaries, or from interviews of the patient or parent/legal guardian if diaries were not kept.

The sponsor also obtained parental assessment of the patient's physical activity at every visit, based on a 5-point scale.

Comments: The efficacy analysis is strictly in accordance with the Written Request. The choice of efficacy parameters and the timing of tests are appropriate. The methodology is well established. (b) (4)

Bone histomorphometry studies often accompany osteoporosis trials. (b) (4)

This should be accompanied by a data analysis plan that includes specific aspects of the histomorphometric study. The data analysis plan must specify statistical methods for treating multiple outcomes that may or may not be independent of each other.

V.7 Safety analyses

As noted above, this study is ongoing. The safety assessment presented in this submission includes all safety data that the sponsor collected by the cutoff date (June 11, 2002). This included all post-Month 12 data[9].

[9] The sponsor determined, after the cutoff date, that four serious AEs (associated with OI surgery) that began prior to that date had not been reported because the investigators considered them to be directly associated with the patient's OI and erroneously believed that they did not need to be reported. The sponsor updated the database in November 2002 to add these four serious AEs. Narratives for these 4 cases (AN 277 at Site 002; AN 385 at Site 011; ANs 401 and 405 at Site 012) are in Section 8.3.2 of the submission.

The analysis of safety was based on the recording of clinical and laboratory AEs and concomitant medications. In addition to these standard safety procedures, the sponsor conducted a number of other assessments that are important for a pediatric population with OI. These included disease-specific clinical evaluations; complete blood counts at every visit; recording standing and sitting height, arm span, and weight; and histomorphometric analysis of iliac crest bone biopsies. In addition, AP and lateral radiographs of all long bones were examined by the central panel of central radiologists for evidence of fracture malunion. Definitions and grading of AEs, including definitions of serious AEs are presented in the submission. These are standard for clinical trials

Fractures

Patients with OI frequently experience fractures, bone pain, and bone deformities. Therefore, the sponsor established specific guidelines for the recording of these events as AEs. Fractures constituted a secondary efficacy endpoint, and all fractures were recorded on a Fracture Report Form to permit their tabulation. Accordingly, the investigators were not required to report fractures as a safety AE in this study, even if the fracture resulted in hospitalization (such occurrences would normally be recorded as serious AEs).

Similarly, symptoms associated with a clinically diagnosed fracture (e.g., bone pain) were not required to be recorded. However, investigators were required to record new or chronic bone pain that worsened during the study and was not associated with a clinically diagnosed fracture.

Fracture healing:

Long-bone radiographs of new fractures seen at Month 12 were examined (by the central radiologists) for malunion (union in an unacceptable position), non-union (absence of healing over at least a three-month period between radiographs), or abnormal callus formation.

Special OI examination:

Investigators conducted clinical OI status evaluations at baseline and every three months at each clinic visit. The following were recorded: dietary intake of calcium, and calcium and vitamin D supplementation; standing and sitting height, arm span, and weight; type of orthoses currently used, if any; concomitant medications; parental assessment of physical activity; assessment of bone pain; and whether surgery for bone deformities had taken place in the previous 3 months.

Assessments of pubertal development (Tanner staging) were also conducted.

An eye examination was required if any ocular symptoms were reported.

Safety histomorphometry examinations:

Iliac crest biopsies, following double tetracycline labeling, were obtained on all patients at baseline and after 24 months of therapy. The following six measures relating to cancellous bone were obtained. The first five relate to cancellous bone formation and the sixth is a measure of cancellous bone resorption:

1. Osteoid volume/bone volume
2. Osteoid surface/bone surface
3. Osteoid thickness
4. Mineralizing surface/bone surface
5. Mineral apposition rate
6. Eroded surface/bone surface (this is a measure of cancellous bone resorption).

V.8 Statistical considerations

The sponsor presents a power analysis that is based on three assumptions (see below). Based on these assumptions, the sponsor calculates that the study had 99% power to detect the superiority of alendronate over placebo (in change from baseline in lumbar spine BMD z-score), using a 2-sided test with an overall Type 1 error = 5%. The three assumptions were:

1. The treatment difference with respect to the change from baseline in lumbar spine BMD z-score was equal to 1 in favor of alendronate.

2. The within-treatment standard deviation with respect to the change from baseline at Month 12 in lumbar spine BMD z-score was equal to 1.

3. The primary efficacy analysis would include approximately 48 and 16 subjects in the alendronate and placebo groups, respectively, following the modified intention-to-treat-LOCF analysis (MITT-LOCF, described below) performed on the early randomization subset in the interim analysis. In addition, approximately 90 and 30 subjects in the alendronate and placebo groups respectively would be included in the analysis of the same variable, using the MITT-LOCF approach performed for the Final Analysis.

Plans for handling missing data and dropouts:

The sponsor planned to employ several approaches to deal with potential missing data and patient dropouts: a MITT-LOCF approach (described below); a data-as-observed approach; and, for the primary efficacy endpoint only, the longitudinal approach.

The MITT-LOCF approach (in which a number of patients were excluded from the analysis, for reasons described below) was used primarily in the analysis of the change from baseline at Month 12 in LS BMD z-score[10].
However, the data cutoff date for the Final Analyses enabled all patients to contribute Month 12 data (except those who discontinued prior to this visit); consequently, the sponsor did not perform a final analysis based on the Early Randomized Subset. The sponsor used the MITT-LOCF-Early Randomized Subset for the primary efficacy outcome in the Interim Analysis.

An interim safety and efficacy analysis was conducted in the latter part of 2001. Adverse experience data were further summarized in the first quarter of 2002. These reports were reviewed by the DSMB.

The primary outcome (BMD z-score) was assessed in both the Interim and the Final Analysis. Consequently the sponsor performed an adjustment for multiplicity, in order to maintain the overall Type 1 error at 5% (this adjustment is detailed in the DAP). For the primary efficacy variable, the sponsor used a two-sided test at the nominal significance levels of 1.0% for the Interim Analysis and 4.8%, for the Final Analysis.

The actual sample sizes for both analyses were 56 ALN and 20 PBO patients in the Interim Analysis and 86 ALN and 26 PBO patients in the Final Analysis. This permitted maintenance of the overall Type 1 error at 5%, using the above two nominal significance levels. This is consistent with the Written Request

Subgroup analyses: For the primary efficacy endpoint at Month 12, The sponsor evaluated treatment-by-subgroup interactions to explore the constancy of treatment effect across pre-defined groups: gender; race, age category (<12 years old; ≥12 years old), OI disease type, and pubertal status.

Changes in conduct of the analysis are described in detail in the submission. These are in accord with agreements made with the Division and appear in protocol amendments and/or amendments to the DAP. They include specification of “Month 12” and “Month 24” (in terms of day ranges, differentiation of Day 365 for a given patient from the end of the first year of the overall study, and similar issues) and descriptions of which data sets appear as “Month 12” or “Month 24” results. Of importance, results up to Month 12 are provided for all efficacy endpoints, and results up to Month 24 are provided for all safety endpoints (clinical and laboratory), concomitant therapies and compliance rates. For the safety, compliance, and concomitant therapy data, the sponsor assessed all data entered into the databases by the data cutoff date. The sponsor uses the phrase “Results up to Month 24” to designate the results of these analyses.

The primary efficacy endpoint (L1-L4 BMD z-score at Month 12) was the difference between the actual BMD measurement and the average BMD for age-matched healthy children. This difference is expressed in terms of numbers of

[10] A complete description of these statistical approaches is in Section VII.G. of the DAP.

standard deviations. The lumbar spine BMD z-scores were obtained directly from the Hologic densitometers and are based on data previously published (Southard et al., 1991).

The sponsor used an ANCOVA model to analyze the changes in BMD. The model included factors for treatment, study center, weight stratum, and baseline BMD. The difference between the ALN and PBO groups was estimated by the difference in least squares mean from the model, and its 95% CI was calculated.

VI Results: Populations enrolled/randomized, patient disposition, concomitant medications, and compliance

VI.1 Populations enrolled/randomized

A total of 139 patients were enrolled into the study[11]. Of these, 122 (87.8%) completed the first 12 months of double-blind treatment. Seventeen patients (12.2%) discontinued up to Month 12: 16 (14.7%) ALN and 1 (3.3%) in PBO. Four ALN patients (3.7%) and no PBO patients discontinued due to a clinical or laboratory AE. A listing of all patients who discontinued up to Month 12, along with the reasons for discontinuation, is provided in the submission. The disposition of patients up to Month 12 is provided in the sponsor's table:

Patient Disposition
Results up to Month 12

	Alendronate (N=109)		Placebo (N=30)	
	n	(%)	n	(%)
ENTERED DOUBLE-BLIND PERIOD:	109		30	
Age range (years)	4 to 19		4 to 18	
COMPLETED UP TO MONTH 12:	93	(85.3)	29	(96.7)
DISCONTINUED ON OR BEFORE MONTH 12:	16	(14.7)	1	(3.3)
Clinical adverse experience†	3	(2.8)	0	(0.0)
Laboratory adverse experience	1	(0.9)	0	(0.0)
Lack of efficacy	1	(0.9)	1	(3.3)
Lost to follow-up	3	(2.8)	0	(0.0)
Patient moved	1	(0.9)	0	(0.0)
Patient withdrew consent	3	(2.8)	0	(0.0)
Protocol deviation	1	(0.9)	0	(0.0)
Discontinued to other reason‡	3	(2.8)	0	(0.0)

Disposition of patients up to Month 24: Nineteen ALN (17.4%) and 3 PBO patients (10.0%) discontinued up to Month 24 (between-group difference p=0.408). Up to Month 24, the percent of patients who discontinued due to a clinical or laboratory AE did not differ significantly between treatment groups: 5

[11] The terms "randomized" and "enrolled" are used interchangeably by the sponsor and designate all patients who were assigned an AN, given one or more bottles of double-blind study medication, and who returned at least one opened bottle. The terms also include those who were dispensed one or more bottles of double-blind medication and returned none of them, in which case they were considered to have taken one tablet of study medication.

(4.6%) for ALN and 1 (3.3%) in PBO. Other reasons for discontinuation were also similar between the groups. The sponsor provides a listing of all patients who discontinued from Month 12 to Month 24, together with the reasons for discontinuation, in the submission.

In the safety analysis, the sponsor included all patients who received at least one dose of study drug. For the primary efficacy analysis, the sponsor used a MITT-LOCF approach, in which missing values were imputed by use of the last on-treatment observation. The sponsor also assessed the primary efficacy variable using both data-as-observed and per-protocol approaches.

To be included in the MITT-LOCF analysis, a patient must have had a baseline and at least one post-baseline LS BMD measurement. Of the 139 patients who received at least 1 dose of study drug, 27 (19.4%) were excluded from any of the three analytic approaches: 23 (21.1%) in ALN and 4 (13.3%) in PBO.

The sponsor lists the reasons for exclusion of these patients. I have reproduced these reasons *verbatim*[12]*:*

_ 2 alendronate patients and 1 placebo patient had their baseline lumbar spine scan conducted on a Lunar densitometer instead of a Hologic densitometer (alendronate: ANs 287 and 288 at Site 002 and placebo: AN 253 at Site 002);
_ 1 alendronate patient was unevaluable due to scoliosis (AN 416 at Site 013);
_ 4 alendronate patients had their baseline lumbar spine scan conducted on a Hologic 2000 model densitometer and their Month 6 lumbar spine scan conducted on a Hologic 4500 model densitometer, and 1 of the 2 machines was sold before a cross-calibration between the machines could be conducted (ANs 088, 091, 307, and 320 at Site 005);
_ 4 alendronate and 2 placebo patients had metallic hardware present in the spine either at baseline and/or at Month 6 (alendronate: AN 321 at Site 006; AN 382 at Site 009; AN 347 at Site 014; and AN 423 at Site 017; placebo: AN 404 at Site 012, and AN 421 at Site 017);
_ 2 alendronate patients and 1 placebo patient had their baseline lumbar spine BMD data stored on an optical disk from which those data could not be retrieved (alendronate: ANs 019, and 269 at Site 002; placebo: 286 at Site 002); and
_ 10 alendronate patients discontinued from the study before their Month 6 lumbar-spine scan was conducted. Their site numbers, ANs, and corresponding reasons for discontinuation are: Site 002, AN 254 refused to return for Month 6 visit, Site 003, AN 060 discontinued due to a clinical

[12] **Comments: These exclusions have been carefully reviewed, both for accuracy of scientific evaluation of the trial results and to determine whether the sponsor fulfilled the requirements of the Written Request. I have concluded that the exclusions were justified and that the remaining numbers of ALN and PBO patients were sufficient to meet the criteria established in the Written Request. Inclusion of data from the first four categories would most likely have increased the variability of the outcome data, with some change in the point estimate but no change in the significance of the treatment comparison.**

adverse experience, Site 005, ANs 087 and 319 were lost to follow-up, and AN 305 moved; Site 008, AN 366 withdrew consent; Site 012, AN 150 withdrew *consent; Site 014, AN 004 was unable to continue due to family reasons, and ANs 346 and 348 discontinued due to a clinical adverse experience. More information regarding these discontinuations is in [4.2.1].*
_ AN 346 at Site 014, who discontinued from the study before her Month 6 lumbar spine scan was conducted (counted in previous paragraph), was improperly positioned during her baseline lumbar spine BMD scan and also had metal sutures in her spine at baseline. This patient was also found to have fibrous dysplasia and not OI when her baseline bone-biopsy specimen and her blood sample, obtained for genetic analysis, were analyzed by the central laboratory (b) (4)

The MITT-LOCF analysis was performed on the remaining 112 patients.

Of these 112 patients, 15 did not have a Month 12 lumbar spine BMD measurement: 12 in ALN and 3 in PBO. These were included in the MITT-LOCF analysis (by carrying forward the Month 6 measurement), but not in the data-as-observed approach. This analysis was applied to the subset of 97 patients who had a Month 12 BMD measurement: 74 (67.9%) ALN and 23 6.7%) PBO. The per-protocol analysis dropped an additional six patients, who violated the "off-drug rule" before the Month 12 time point, by missing more than 25% of the doses of study medication.

The following table displays the number of patients included in each analytical subset.

Number of Patients (%) in the Lumbar Spine BMD Analysis at Month 12

	Alendronate (N=109)		Placebo (N=30)		Total (N=139)	
	n	(%)	n	(%)	n	(%)
Included in the MITT-LOCF analysis†	86	(78.9)	26	(86.7)	112	(80.6)
With data in the Month 12 day range	74	(67.9)	23	(76.7)	97	(69.8)
With data carried-forward from the Month 6 day range	12	(11.0)	3	(10.0)	15	(10.8)
Included in the data-as-observed analysis	74	(67.9)	23	(76.7)	97	(69.8)
Included in the per-protocol analysis	68	(62.4)	23	(76.7)	91	(65.5)

† Primary analysis set.
Alendronate: Alendronate 5 mg or 10 mg daily.
Placebo: Placebo for alendronate 5 mg or 10 mg daily.
MITT: Modified-intention-to-treat.
LOCF: Last-observation-carried-forward.

Protocol deviations

Patients who were excluded from the primary efficacy analysis for reasons relating to use of a particular densitometer or for other technical reasons are discussed above. One patient was subsequently determined to have fibrous dysplasia instead of OI, based on genetic analysis. This patient was excluded

from the efficacy analysis. Six patients violated the “off-drug rule” before the Month 12 time point. One patient started study drug after her 19th birthday. This patient did not have a baseline or any other BMD determination because it was determined that she had metallic hardware in her spine at baseline. She was not included in any of the primary efficacy analyses. This patient did not have any fractures or AEs during the study.

One patient weighed 89.6 kg at baseline and was erroneously randomized to alendronate 5 mg. This patient was not excluded from the per-protocol analyses because weight at baseline was not a prespecified exclusionary criterion for this analysis.

Day ranges: Since patient visits did not always occur precisely on the day that was specified in the protocol, the sponsor established day ranges relative to the start of treatment period for analyses of the following outcomes: BMD, grip strength and PEDI scores, anthropometric and pain measurements, x-ray assessments, and biochemical markers of bone turnover. The day ranges are presented in the submission. For BMD, the six-month range = 23-274 days and the 12 month range = 275-456 days.

The relative day ranges for each of the efficacy outcomes are presented in the following table:

Relative Day Ranges

Time Point	BMD	Grip Strength and PEDI measurements	Biochemical Markers†	Anthropometric and Pain Measurements	X-ray
Baseline	≤22	≤2	≤1	≤2	≤1
Month 3	--	--	2 to 137	3 to 137	--
Month 6	23 to 274	3 to 274	138 to 228	138 to 228	--
Month 9	--	--	229 to 319	229 to 319	--
Month 12	275 to 456	275 to 456	320 to 411	320 to 411	2 to 548

† Weekly day ranges were also established for urine NTx, and calcium/Cr data collected once a week for the first 3 months of the each patient’s participation in the study.

Comments: These ranges are quite broad and may reduce the confidence one may have in the timing of efficacy responses. However, they will not substantially affect the analyses of treatment-related differences in responses to randomized, double-blind treatment.

VI.1.1 Demographic and other baseline characteristics

Of the 139 randomized patients, 108 (77.7%) were in weight Stratum I (and given alendronate 5 mg or matching PBO) and 31 (22.3%) were in Stratum II and given alendronate 10 mg or matching PBO. Within each treatment group (ALN or PBO), the percent of patients distributed between the weight strata was essentially the same. The sponsor lists the major baseline and demographic characteristics of the patients, by treatment group, in the following table:

	Alendronate (N=109)	Placebo (N=30)	Total (N=139)
	n (%)	n (%)	n (%)
Gender			
Male	62 (56.9)	16 (53.3)	78 (56.1)
Female	47 (43.1)	14 (46.7)	61 (43.9)
Age (Years)			
<12	55 (50.5)	15 (50.0)	70 (50.4)
≥12	54 (49.5)	15 (50.0)	69 (49.6)
N	109	30	139
Mean	11.0	11.1	11.0
SD	3.6	4.0	3.7
Median	11.0	11.5	11.0
Range	4 to 19	4 to 18	4 to 19
Race			
White	88 (80.7)	25 (83.3)	113 (81.3)
Black	6 (5.5)	2 (6.7)	8 (5.8)
Asian	2 (1.8)	0	2 (1.4)
Multiracial	1 (0.9)	0	1 (0.7)
Hispanic	11 (10.1)	1 (3.3)	12 (8.6)
Indian	1 (0.9)	1 (3.3)	2 (1.4)
Native American	0	1 (3.3)	1 (0.7)
Pubertal Status			
Prepuberal	51 (46.8)	12 (40.0)	63 (45.3)
Pubertal	58 (53.2)	18 (60.0)	76 (54.7)
Type of Osteogenesis Imperfecta			
	(n=109)	(n=30)	(n=139)
Type I	26 (23.9)	6 (20.0)	32 (23.0)
Type II	32 (29.4)	7 (23.3)	39 (28.1)
Type IV	37 (33.9)	17 (56.7)	54 (38.8)
Type Unknown	13 (11.9)	0	13 (9.4)
Type Not Recorded	1 (0.7)	0	0

Alendronate: Alendronate 5 or 10 mg daily.
Placebo: Placebo for alendronate 5 or 10 mg daily.
SD: Standard deviation.

A total of 123 patients had valid baseline lumbar spine BMD measurements, with far fewer patients having baseline measurements at other anatomical sites. The baseline BMD measurements are presented in the following table:

	Alendronate (N=109)	Placebo (N=30)	Total (N=139)
Lumbar Spine BMD z-Score			
N	97	26	123
Mean	-4.50	-4.56	-4.51
SD	1.45	1.61	1.48
Median	-4.50	-4.75	-4.50
Range	-7.4 to -1.2	-7.9 to -1.2	-7.9 to -1.2
Lumbar Spine BMD (g/cm^2)			
N	97	26	123
Mean	0.374	0.364	0.372
SD	0.162	0.157	0.160
Median	0.369	0.342	0.355
Range	0.08 to 0.85	0.17 to 0.71	0.08 to 0.85
Femoral neck BMD (g/cm^2)			
N	10	2	12
Mean	0.506	0.428	0.493
SD	0.151	0.060	0.141
Median	0.555	0.428	0.551
Range	0.27 to 0.68	0.39 to 0.47	0.27 to 0.68
Total Hip BMD (g/cm^2)			
N	10	2	12
Mean	0.534	0.448	0.520
SD	0.185	0.013	0.171
Median	0.564	0.448	0.502
Range	0.23 to 0.78	0.44 to 0.46	0.23 to 0.78
Alendronate: Alendronate 5 mg or 10 mg daily. Placebo: Placebo for alendronate 5 mg or 10 mg daily. SD: Standard deviation. z-Score: The number of SDs from the mean for age-matched healthy controls.			

Comments: The degree of osteopenia in this population is striking. Note the lower end of the ranges of BMD in gm/cm2.

Baseline fractures: One hundred patients (73.0%) had from 1 to 25 fractures during the year before the study, based on reports from the patient or guardian. Data on fracture history prior to the study are provided in the following table:

	Alendronate (N=109)	Placebo (N=30)	Total (N=139)
	n (%)	n (%)	n (%)
At Least One Fracture Experienced During the Year Before the Study, as Reported by the Patient			
	(n=107)	(n=30)	(n=137)
Yes	77 (72.0)	23 (76.7)	100 (73.0)
No	30 (28.0)	7 (23.3)	37 (27.0)
Number of Fractures Experienced During the Year Before the Study, as Reported by the Patient			
N	107	30	137
Mean	2.0	2.6	2.2
SD	3.0	2.6	2.9
Median	1.0	2.0	1.0
Range	0 to 25	0 to 10	0 to 25
At Least One Fracture Experienced at Any Time Before the Study, as Reported by the Patient			
	(n=107)	(n=30)	(n=137)
Yes	107 (100.0)	30 (100.0)	137 (100.0)
No	0	0	0
Number of Fractures Experienced at Any Time Before the Study, as Reported by the Patient			
N	107	30	137
Mean	51.6	40.6	49.2
SD	70.8	53.6	67.4
Median	26.0	25.0	25.0
Range	2 to 310	6 to 250	2 to 310
Alendronate: Alendronate 5 mg or 10 mg daily. Placebo: Placebo for alendronate 5 mg or 10 mg daily. SD: Standard deviation.			

Comments: As expected, the fracture rate in this population was extremely high, emphasizing the enormous disease burden that is borne by these patients. The distribution of baseline fracture incidence was evenly distributed between the treatment groups, as shown in the next table:

	Alendronate (N=109)	Placebo (N=30)	Total (N=139)
	n (%)	n (%)	n (%)
Number of Fractures Experienced During the Year Before the Study as Reported by the Patient			
	(n=107)	(n=30)	(n=137)
0	30 (28.0)	7 (23.3)	37 (27.0)
1	28 (26.2)	7 (23.3)	35 (25.5)
2	23 (21.5)	4 (13.3)	27 (19.7)
3	8 (7.5)	4 (13.3)	12 (8.8)
4	6 (5.6)	0	6 (4.4)
5	5 (4.7)	4 (13.3)	9 (6.6)
6	1 (0.9)	2 (6.7)	3 (2.2)
7	2 (1.9)	0	2 (1.5)
8	2 (1.9)	1 (3.3)	3 (2.2)
10	1 (0.9)	1 (3.3)	2 (1.5)
25	1 (0.9)	0	1 (0.7)
Number of Fractures Experienced at Any Time Before the Study as Reported by the Patient			
	(n=107)	(n=30)	(n=137)
0	0	0	0
1 to 10	25 (23.4)	5 (16.7)	30 (21.9)
11 to 20	25 (23.4)	8 (26.7)	33 (24.1)
21 to 30	12 (11.2)	5 (16.7)	17 (12.4)
31 to 40	14 (13.1)	4 (13.3)	18 (13.1)
41 to 50	6 (5.6)	3 (10.0)	9 (6.6)
51 to 60	4 (3.7)	0	4 (2.9)
61 to 80	2 (1.9)	3 (10.0)	5 (3.6)
81 to 100	5 (4.7)	0	5 (3.6)
101 to 110	2 (1.9)	0	2 (1.5)
111 to 140	1 (0.9)	0	1 (0.7)
141 to 220	5 (4.7)	1 (3.3)	6 (4.4)
221 to 300	5 (4.7)	1 (3.3)	6 (4.4)
301 to 310	1 (0.9)	0	1 (0.7)

Baseline radiological assessments, performed by the panel of central radiologists, did not differ appreciably between the two treatment groups. Parameters included mean cortical width (at the midpoint of the second left metacarpal bone), and mean anterior, posterior and midline vertebral heights. The data are presented in Table 17 of the submission.

Bone pain was reported by 89 (64.0%) of patients (or guardian) at baseline. The average number of days per week with bone pain was 2.4 days. Twenty-six (19.4%) patients had bone pain awakening them at night. Data on bone pain appear in Table 18 of the submission. The reports of bone pain were roughly equally distributed between treatment groups.

Anthropometric data are presented in Table of the NDA. I have reproduced part of Table 19 below, in order to give some idea of the patients' body sizes:

	Alendronate (N=109)	Placebo (N=30)	Total (N=139)
Weight (kg)			
N	108	30	138
Mean	31.95	31.94	31.95
SD	18.27	16.76	17.90
Median	28.35	29.20	28.70
Range	10.89 to 96.00	13.21 to 67.20	10.89 to 96.00
Weight z-Score			
N	108	30	138
Mean	-1.12	-0.94	-1.08
SD	1.49	1.78	1.55
Median	-1.33	-1.18	-1.31
Range	-3.78 to 3.32	-3.80 to 3.96	-3.80 to 3.96
Height (cm)			
N	106	25	131
Mean	120.8	121.7	121.0
SD	24.6	23.1	24.2
Median	118.9	118.1	118.4
Range	76.0 to 176.6	87.0 to 170.0	76.0 to 176.6
Height z-Score			
N	106	25	131
Mean	-3.60	-3.39	-3.56
SD	3.36	3.09	3.30
Median	-2.87	-2.76	-2.80
Range	-14.16 to 1.19	-11.09 to 2.20	-14.16 to 2.20
Body Mass Index (kg/m^2)			
N	106	25	131
Mean	20.85	20.07	20.70
SD	6.91	5.06	6.59
Median	18.52	18.19	18.47
Range	12.12 to 45.07	13.97 to 32.02	12.12 to 45.07

The BMI z-scores corresponding to these BMIs are about 0.69, which were also evenly distributed between the treatment groups.

Baseline Pediatric Evaluation of Disability Inventory scores are summarized in Table 20 of the NDA. At baseline, 42.9% and 40.0%, respectively, had functional skill and caregiver assistance self-scare scaled scores of <100 (100 is the maximum value). In addition, 71.4% and 57.7%, respectively, had functional skill and caregiver assistance mobility scaled scores of <100. Data on grip strength are given, by treatment group, in Table 22 of the submission. A review of these data relating to function showed that there was no meaningful treatment-group related difference in any parameter at baseline.

Baseline parameters relating to mineral metabolism are presented in Table 23 of the submission. These parameters included serum calcium, phosphorus, creatinine, total alkaline phosphatase, PTH, vitamin D metabolites, urine NTX/Cr, and urinary c-AMP. These did not differ between treatment groups at baseline.

Iliac crest biopsies for bone histomorphometry were available from 10 patients by the data cutoff date for this report (June 11, 2002). The data for these 10 patients are summarized in the sponsor's Table 24, not reproduced here.

Prior drug therapies All prior drug therapies used by any of the 139 randomized patients, with an incidence of at least 5% in either treatment group are summarized in Table 25 of the submission. Most patients (96.4%) reported using

at least one prior therapy. A total of 24 (17.3%) and 18 (12.9%) had taken vitamins and mineral supplements, respectively; 52 patients (37.4%) had taken anti-inflammatory drugs; and 118 (84.9%) had taken analgesics; 8.3% of ALN and 6.7% of PBO had taken systemic corticosteroids. There were no meaningful between-group differences in the incidence of any prior drug therapy.

Calcium and vitamin D :

At baseline, the investigators questioned all patients about current intake of dietary calcium, calcium supplements, and vitamin D[13]. The average daily calcium intake from dietary sources and supplements was similar in the treatment groups, as was the average vitamin D intake from dietary sources.

For dietary calcium, the average baseline daily dose among the 76 patients who responded to the question was 713.7 mg. Only 18 (15.5%) of the 116 patients who responded were taking calcium supplements, at an average daily dose of 429.6 mg, at baseline. Among the 115 patients who responded, only 12 (10.4%) were actually taking vitamin D supplements, at an average daily dose of 397.3 mg (median of 400 mg). There were meaningful between-group differences in baseline consumption of calcium or vitamin D. However, the ranges were quite broad (Table 26 of the NDA, not reproduced here).

VI.1.2 Concomitant drug therapies

This category consists of drugs that were taken during the double-blind treatment period. The majority of 139 randomized patients (129 or 92.8%), took at least one concomitant medication up to Month 12. There were no meaningful between-group differences in use of concomitant therapies. A minority of patients (about 6%) took systemic corticosteroids and there was widespread use of analgesic agents (summary, by treatment group, in Table 27, not reproduced here).

Concomitant calcium and vitamin D use, derived from diet and supplements, was assessed by questioning patients at each study visit. The dietary intake of calcium and vitamin D from both sources was similar in both treatment groups (mean daily calcium was about 670 mg for both groups). About 45-50% of patients in each treatment group took a dietary calcium supplement at least once during the double-blind treatment phase.

Among respondents to the question regarding the intake of vitamin D supplements, about 33% took at least one dose of vitamin D supplements in each treatment group. The mean average daily dose of vitamin D during this period was 63.0 IU in ALN and 44.5 IU in PBO. Details regarding concomitant calcium and vitamin D intake are presented in Table 28 of the NDA.

VI.1.3 Treatment compliance

[13] The RDA for calcium in children ages 4 to 8 is 800 mg/day; in children ages 9 to 18, the RDA is 1300 mg/day. The recommended intake of vitamin D in children 4 to 18 is 200 IU/day (Food and Nutrition Board, Institute of Medicine and National Academy of Sciences).

Treatment compliance up to Month 12, by group, is shown in Table 29 of the submission. Compliance rates were defined as (the number of days in which study drug was taken/total number of days) X 100. The compliance rates were 92.5% and 94.6% in ALN and PBO, respectively.

VII Efficacy outcomes

VII.1 Primary efficacy outcome: change in lumbar spine BMD z-score

The primary efficacy outcome was change from baseline at Month 12 in lumbar spine BMD z-score using the MITT-LOCF statistical analysis. At baseline, both ALN and PBO had a mean L1-L4 BMD z-score of -4.6. As shown in the next table, there was a highly significant ($p<0.001$) mean increase from baseline to Month 12 in ALN. The increase was equal to 0.99 z-score units. In contrast, there was a statistically non-significant ($p>0.05$) increase in mean BMD from baseline in PBO at Month 12. The increase in PBO was equal to 0.09 z-score units.

The treatment-group difference at 12 months was highly significant ($p<0.001$ for comparison ALN vs PBO BMD z-score increase from baseline). The treatment-group difference in LS means change from baseline was 0.92 (0.62, 1.22, 95% CI) z-score units in favor of ALN. The analysis did not detect any treatment-by-center, treatment-by-stratum, or treatment-by-baseline BMD z-score interaction.

These data are summarized in the following table:

Change From Baseline at Month 12 in Lumbar Spine BMD z-Score
Modified-Intention-to-Treat Last-Observation-Carried-Forward Approach

Treatment	N	Means (Observed)		Change From Baseline			
		Baseline	Month 12	Mean†	SE	Adjusted Mean‡	LSD 95% CI
Alendronate	86	-4.6	-3.6	0.99***	0.08	1.02	(0.83, 1.22)
Placebo	26	-4.6	-4.5	0.09	0.11	0.10	(-0.18, 0.38)
Between-treatment group comparison							
Adjusted mean§				0.92			
95% CI (adjusted mean)				(0.62, 1.22)			
p-Value				<0.001¶			

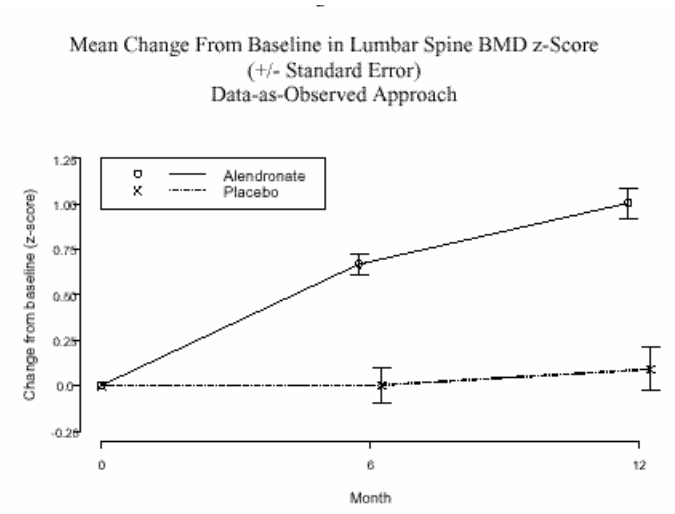
† Within-treatment test of mean=0: ***:p≤0.001.
‡ Adjusted for center, stratum and baseline lumbar spine BMD z-score.
§ Positive mean treatment differences are in favor of alendronate.
¶ This observed p-value was inferior to the nominal significance level for the Final Analysis (0.048).
Alendronate: Alendronate 5 mg or 10 mg daily.
Placebo: Placebo for alendronate 5 mg or 10 mg daily.
SE: Standard error.
LSD: Least squares mean difference.
CI: Confidence interval.
z-Score: The number of standard deviations from the mean for age-matched healthy controls.

Comments: The primary efficacy objective has clearly been achieved. The treatment-related changes are quite substantial, in terms of both absolute and percent changes in BMD from baseline. The increase of about 1 z-score SD unit, from –4.6 to –3.6, that was seen in the alendronate group corresponded to an absolute BMD gain of about 0.1 gm/cm^2. Since the baseline BMD was very low (about 0.375 gm/cm^2), this represented a 30% change over 12 months. It is interesting that in most studies of the effects

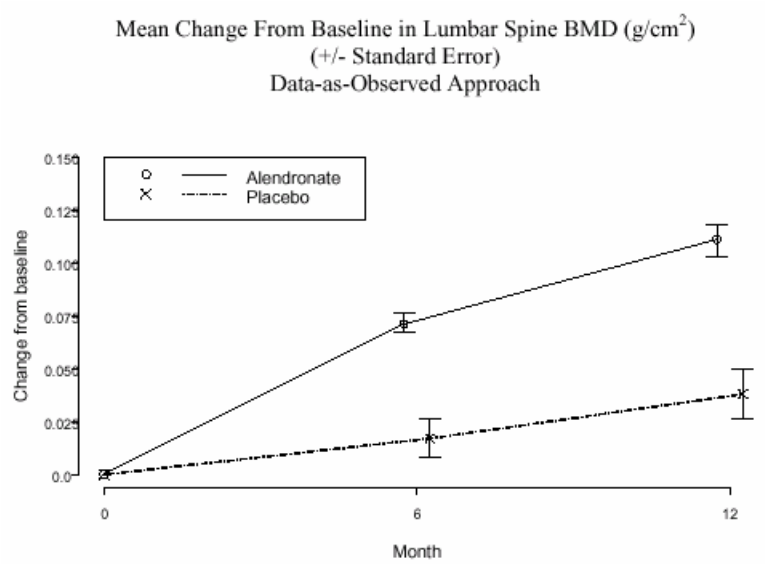
of alendronate (or other active agents) in postmenopausal osteoporosis, the absolute mean increases in lumbar spine BMD have been approximately the same (or somewhat less, depending on the trial) over three years. However, in these trials, the baseline BMD levels have averaged around 0.7 gm/cm^2. Consequently, the percent increases have been about 5-7% within the first 1-2 years of studies in postmenopausal osteoporotic women. Since alendronate is not an anabolic agent, the results of the present study suggest that the fractional turnover rate of bone mineral is much higher in children with OI than in postmenopausal women with osteoporosis. Other factors, such as natural bone growth in a pediatric population, may have contributed to the overall effectiveness of an anti-resorptive agent. As will be seen below, additional analyses of these data strongly suggest that alendronate treatment is associated with an increase in mineralization in the growing bones of children with OI.

These results using the MITT-LOCF approach were in accord with those obtained with the other analytical approaches (data-as-observed, per-protocol, and longitudinal). As presented in the NDA, significant ($p<0.001$) mean increases from baseline of 1.00, 1.04, and 1.00 z-score units were observed in ALN, using the data-as-observed, per-protocol, and longitudinal statistical approaches, respectively. For PBO, the three additional statistical approaches demonstrated a non-significant ($p>0.050$) mean increase from baseline of 0.09 z-score SD units. Furthermore, the three analytical approaches yielded treatment differences in LS means between ALN and PBO of 0.98, 1.00, and 0.94 z-score units, in favor of ALN ($p<0.001$).

Using the data-as-observed approach, the mean changes from baseline in LS BMD z-score during the 12-month period are shown in the figure below:



Changes in bone density expressed as gm/cm^2: When expressed as changes in gm/cm^2, the data demonstrate similar treatment group differences at six and twelve months:



Effect of body weight/dose: There was essentially no difference in outcome according to weight stratum. In Stratum I, 12 months of treatment with ALN 5 mg or PBO increased LS BMD z-scores by 1.03 and 0.04 units, on average, respectively. In Stratum II, treatment with ALN 10 mg or PBO for 12 months increased LS BMD z-score by 0.81 and 0.25 units, respectively. The treatment differences did not differ significantly according to stratum (treatment by stratum interaction: p>0.050).

Responder analysis: The sponsor also analyzed the proportions of patients in ALN and PBO whose changes in LS BMD z-score at Month 12 exceeded pre-specified thresholds, ranging from -0.50 to 2.00 in increments of 0.25 z-score units. In PBO, 58% of the patients had an increase in LS BMD z-score from baseline at Month 12, versus 93% of ALN. An increase in LS BMD z-score that exceeded one unit was observed in 43% of ALN, compared with none in PBO.

The data are presented in the following table:

Percentage of All Patients With Change from Baseline at Month 12 in BMD z-Score Exceeding a Specified Threshold
Modified-Intention-to-Treat Last-Observation-Carried-Forward Approach

Treatment	N	Threshold (in BMD z-Score Unit)										
		-0.50	-0.25	0.00	0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00
		Percentage of Patients Exceeding the Specified Threshold[†]										
Alendronate	86	99%	99%	93%	83%	74%	60%	43%	31%	21%	14%	12%
Placebo	26	81%	77%	58%	50%	12%	8%	0%	0%	0%	0%	0%

[†] Percentage of patients with a change from baseline at Month 12 in lumbar spine BMD z-score greater than the specified threshold.
Alendronate: Alendronate 5 mg or 10 mg daily.
Placebo: Placebo for alendronate 5 mg or 10 mg daily.

The sponsor also provides data on estimated changes in lumbar spine BMC, expressed both as percent and absolute changes in bone mineral content at baseline and at six and twelve months. Using the MITT-LOCF approach, the ALN group gained almost 50% in BMC from baseline at 12 months, whereas PBO gained an average of about 18% during this period. The absolute increases were estimated to be about 5 gm for ALN and about 2.6 gm for PBO. The data are presented in the sponsor's table below:

Percent Change From Baseline at Month 12 in Lumbar Spine BMC (g)
Modified-Intention-to-Treat Last-Observation-Carried-Forward Approach

Treatment	N	Means (Observed)		Percent Change From Baseline			
		Baseline	Month 12	Mean[†]	SE	Adjusted Mean[‡]	LSD 95% CI
Alendronate	86	13.4	18.3	49.3***	4.3	45.8	(35.3, 56.3)
Placebo	26	13.4	16.0	18.2***	4.4	13.8	(-1.4, 28.9)
Between-treatment group comparison							
Adjusted mean[§]				32.1			
95% CI (adjusted mean)				(15.8, 48.4)			
p-Value				<0.001			

[†] Within-treatment test of mean=0: ***:p≤0.001.
[‡] Adjusted for center and stratum.
[§] Positive mean treatment differences are in favor of alendronate.
Alendronate: Alendronate 5 mg or 10 mg daily.
Placebo: Placebo for alendronate 5 mg or 10 mg daily.
SE: Standard error.
LSD: Least square difference.
CI: Confidence interval.

Analyses of subgroups

As an exploratory analysis, treatment-by-subgroup interactions were examined in order to assess consistency of treatment effect across five pre-defined subgroups: gender, race [white or other], age [< or ≥ 12 years], OI disease type, [Type I vs all others], and pubertal status. Subgroups were examined only if there were at least six patients in ALN and two in the corresponding PBO group.

According to this analysis, the treatment effect was consistently in favor of ALN. The mean LS BMD z-score changes from baseline at Month 12 ranged from 0.82 to 1.24 units in ALN, compared to a range of -0.06 to 0.18 units in PBO. Treatment differences were consistent across subgroups, as indicated by lack of significant ($p>0.050$) subgroup-by treatment interactions.

A further exploratory analysis examined the consistency of the treatment difference across baseline levels of various parameters, including LS BMD z-score, presence of fracture during the year prior to the study, biochemical markers of bone turnover**,** height, weight, and BMI z-score. Across these categories, mean changes from baseline at Month 12 in LS BMD z-score ranged from 0.73 to 1.23 units in ALN, compared to -0.28 to 0.32 units in PBO, indicating a treatment difference that was consistently in favor of ALN. Further details of this exploratory analysis are provided in the submission.

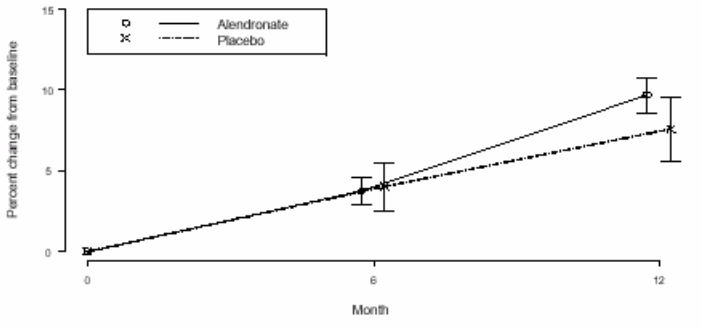
Changes in lumbar spine BMD at Month 6: Using the MITT-LOCF approach, there was a significant ($p<0.001$) mean percent increase from baseline of 24.5% in ALN, compared to a non-significant ($p>0.05$) increase of 5.1% in PBO. At six months, the treatment-related difference was significant ($p<0.001$), with treatment difference in LS means of 19% (9.0%, 29.8%, 95% CI). There was no significant treatment-by-stratum interaction. An analysis of absolute changes in LS BMD at six months yielded similar results. In ALN, BMD increased by 0.07 g/cm^2 (from 0.37 to 0.44 g/cm^2), compared to an increase of 0.02 g/cm^2 (from 0.37 to 0.39 g/cm^2) in PBO. Identical results were obtained using the data-as-observed approach.

The sponsor also analyzed changes in lumbar spine BMC at six months, with similar within- and between-group results (data in NDA).

Lumbar spine area: The sponsor provides estimates of changes in LS area, using both the MITT-LOCF and data-as-observed approaches. Within-treatment estimates of the mean percent change from baseline were adjusted for center, stratum, and treatment assignment using an ANOVA model. The treatment difference between ALN and PBO was estimated by the difference in LS means from the model, and its 95% CI was calculated.

The mean percent changes in LS area at baseline, Month 6 and Month 12 are plotted for each treatment group in the following figure:

Mean Percent Change From Baseline in Lumbar Spine Area
(+/- Standard Error)
Data-as-Observed Approach



When graphed as absolute changes in LS area, the results were essentially the same. At Month 12, using the MITT-LOCF approach, there were significant mean increases from baseline in LS area in both treatment groups: 9% ($p \leq 0.001$) for ALN and 6.3% ($p \leq 0.01$) for PBO. There was no significant between-group difference in LS means, although the increase was numerically greater in ALN. The data are summarized in the following table:

Percent Change From Baseline at Month 12 in Lumbar Spine Area (cm^2)
Modified-Intention-to-Treat Last-Observation-Carried-Forward Approach

Treatment	N	Means (Observed)		Percent Change From Baseline			
		Baseline	Month 12	Mean†	SE	Adjusted Mean‡	LSD 95% CI
Alendronate	86	32.2	34.9	9.0***	1.0	7.8	(4.9, 10.7)
Placebo	26	32.7	34.9	6.3**	1.9	5.5	(1.4, 9.7)
Between-treatment group comparison							
Adjusted mean§				2.3			
95% CI (adjusted mean)				(-2.2, 6.8)			
p-Value				0.312			

† Within-treatment test of mean=0: ***:$p \leq 0.001$, **:$p \leq 0.010$.
‡ Adjusted for center and stratum.
§ Positive mean treatment differences are in favor of alendronate.

The results at Month 12 were similar when analyzed by the data-as-observed approach (data in NDA, not shown here).

The sponsor also presents an analysis of the proportions of patients in each treatment group whose percent changes in LS area approximated pre-specified values. The LS area remained constant or decreased in 10% of ALN and 31% of PBO patients at Month 12. The percent decrease from baseline at Month 12 was equal or larger than 4% in 5% of ALN and 15% of PBO patients. Details of this responder analysis are presented in the NDA.

Mean absolute increases in LS area are also presented in the submission. At Month 12, using the MITT-LOCF approach, average LS area increased in ALN by 2.7 cm^2 (from 32.2 to 34.9 cm^2), compared to an increase of 2.3 cm^2 (from

32.7 to 34.9 cm^2) in PBO. Similar results were obtained using the data-as-observed approach.

Finally, the sponsor presents the mean percent change in LS area from baseline at Month 6. Using the MITT-LOCF approach, there were significant mean percent increases of 3.8% ($p<0.001$) and 4.1% ($p<0.050$) at Month 6 in ALN and PBO, respectively. The between-treatment difference was not significant ($p=0.586$). Mean absolute increases in LS area at Month 6 (MITT-LOCF) were 1.2 cm^2 (from 32.5 to 33.7 cm^2) in ALN, and 1.2 cm^2 (from 33.4 to 34.6 cm^2) in PBO. Identical results were obtained using the data-as-observed approach.

Comments: This study has clearly demonstrated a substantial increase in LS BMD in association with alendronate treatment. Within-group increases from baseline (for both ALN and PBO) and between-group comparisons (ALN vs PBO) were statistically significant and sufficiently robust to withstand three separate statistical approaches. In addition to the overall increases in BMD, the responder rate in the alendronate group exceeded that in placebo. Subgroup analyses found no subgroup, including weight stratum, in which the treatment effect was not manifest.

As described above, the fractional increases in BMD as a result of alendronate treatment were well in excess of those that are generally found in studies in adults with osteoporosis. Since alendronate is not an anabolic agent, the data suggest that the underlying bone turnover rates are higher in OI than in PMO, male osteoporosis, or GCIOP. However, it should be noted that other factors, such as primary growth of bone, may also play a role in the impressive increases in lumbar spine BMD that are found in association with alendronate treatment in this pediatric population.

The increases in BMD were accompanied by parallel increases in BMC. The results of statistical analyses of changes in BMC were as robust as for the analyses of BMD. The overall results were essentially the same, whether the response variable was expressed as z-score units, percent BMD/BMC increase, or absolute BMD/BMC increase. Finally, both groups had increases from baseline in LS bone area, which is indicative of skeletal growth, at both six and 12 months. The increases in LS area were the same in both treatment groups.

Overall, the data demonstrate that, relative to placebo, alendronate treatment is associated with an impressive increase in lumbar spine bone mineralization, associated with unimpeded lumbar spine areal bone growth in pediatric patients with OI.

VII.2 Secondary efficacy outcomes

Femoral neck BMD:

This was not a formal endpoint, both for technical reasons and because there are no established pediatric reference values. Patients without evaluable LS

vertebrae (e.g., patients with metallic devices) were required to have femoral neck and total hip BMD, BMC, and area assessments at baseline and every six months thereafter during the double-blind treatment phase. A few additional patients who had evaluable LS vertebrae also had measurements at the femoral neck and hip. As it turned out, only six patients had femoral neck and total hip BMD measurements at Month 12: four in ALN and two PBO. The mean percent changes (95% CI) from baseline in femoral neck BMD were 5.6% (-16.3%, 27.6%) in ALN and 20.4% (-79.7%, 120.5%) in PBO. For total hip, the increases were 18.6% (-5.6%, 42.8%) in ALN and 20.3% (-51.5%, 92.2%) in PBO.

Comments: No conclusions can be made on the basis of these data. It is unfortunate that the sponsor did not obtain hip BMD measurements in all patients, despite potential technical difficulties. The lack of pediatric reference data, which would be needed for determination of z-scores, would have limited the interpretation of raw BMD/BMC data in the pediatric population. On the other hand, this was an internally controlled study, and some useful within- and between-group comparisons might have been made. As it turns out, the radiological fracture data (see below) relate to long bones and the BMD data are restricted to the lumbar spine.

Fracture outcomes

Fracture incidence was a secondary efficacy endpoint. To measure fracture incidence, the sponsor recorded and analyzed radiologically confirmed fractures and investigator-reported fractures.

A) Radiologically confirmed fractures: These were long-bone fractures that occurred from Baseline to Month 12. Radiographs of the upper and lower extremity long bones (AP and/or lateral films of left and right radius, ulna, femur, tibia, and fibula) were obtained at Baseline and Month 12 and examined by a panel of three radiologists (blinded as to treatment allocation). All decisions regarding the presence of a fracture had to be unanimous. To verify reproducibility, 24 patients' x-rays were re-read. In addition another radiologist, also blinded as to treatment allocation, compared fracture locations that were noted at the first and the second readings. Data were analyzed both as fracture rate (during the 12-month period) and the number of patients with at least one new fracture.

B) Investigator-reported fractures: These were fractures that were reported by patients or parents and that occurred between Baseline and Month 12. All reports were judged by the investigators to represent clinical fractures. However, these may or may not have been documented radiologically. The reports included fractures that occurred anywhere in the body. The sponsor evaluated investigator-reported fractures on the basis of both the yearly fracture rate and an analysis of time-to-first fracture.

Results:

A) Radiologically-confirmed fractures

By the data cutoff date for this report, 123 patients had baseline and Month 12 long-bone films read by the radiologists. Two of these failed to have evaluable sets of films at baseline and Month 12 for any of the long bones. Therefore, 121 patients were included in the analysis: 94 in ALN and 27 in PBO.

In this analysis, 52 of the 94 patients in ALN (55.3%) and 13 of the 24 patients in PBO (48.1%) had at least one new radiologically confirmed long-bone fracture at Month 12. The relative risk estimate (ALN/PBO), adjusted for stratum, was 1.15 (0.75, 1.78, 95%CI). There was a significant treatment-by-stratum interaction (p=0.045). In stratum I, the percent of patients with at least one new fracture was 58.9% in ALN and 40.9% in PBO. In Stratum II, the corresponding percentages were 42.9% and 80.0%.

The frequency distribution of the number of new fractures in each treatment group at Month 12 is presented in the next table. About half the patients in each group had no new fractures. The cumulative percentages of patients with multiple new radiologically confirmed long-bone fractures were comparable between the treatment groups. In all, 27.7% of ALN and 29.6% of PBO had >1 fracture.

Frequency Distribution of the Number of New Radiologically Confirmed Long-Bone Fractures Experienced at Month 12

Number of Fractures	Alendronate (N=94)			Placebo (N=27)		
	n	%	(Cum.%)	n	%	(Cum.%)
7	0	0.0	(0)	1	3.7	(3.7)
6	1	1.1	(1.1)	0	0.0	(3.7)
5	3	3.2	(4.3)	0	0.0	(3.7)
4	3	3.2	(7.4)	0	0.0	(3.7)
3	7	7.4	(14.9)	4	14.8	(18.5)
2	12	12.8	(27.7)	3	11.1	(29.6)
1	26	27.7	(55.3)	5	18.5	(48.1)
0	42	44.7	(100.0)	14	51.9	(100.0)

The sponsor also presents the mean number of new radiologically confirmed long-bone fractures per patient, by treatment group in Table 40 of the NDA. There were 104 such fractures in 94 alendronate patients and 30 in 27 PBO patients. The mean number of new fractures was 1.11 in ALN and 1.11 in PBO (p=0.903). There was no significant treatment-by-stratum interaction.

Finally, the sponsor performed two additional analyses of radiological fracture outcomes: a fracture assessment that excluded bones with hardware and a reliability evaluation.

To investigate possible influence of hardware the sponsor performed a sensitivity analysis that repeated the above assessment with the exclusion of all bones with metallic devices that were visible either at baseline or at Month 12. All 121 patients included in this analysis had at least one evaluable long bone without

hardware. The results of this analysis, presented in detail in the NDA, demonstrated no treatment-group difference in the percent of patients with at least one new radiologically confirmed fracture (30.9% in ALN vs 33.3% in PBO, RR 0.94; 0.50, 1.74 95% CI). Although there were significant treatment-by-stratum interactions, there was no significant qualitative interaction[14]. The remainder of this analysis was essentially the same as the analysis that included bones with hardware. The two treatment groups had essentially the same frequency distribution of the number of new fractures and number of new fractures/patient (which were 0.49 in ALN and 0.63 in PBO). The frequency distribution of the number of new fractures is shown in the following table, taken from the sponsor's submission:

Number of Fractures	Alendronate (N=94)			Placebo (N=27)		
	n	%	(Cum.%)	n	%	(Cum.%)
5	0	0.0	(0)	1	3.7	(3.7)
4	1	1.1	(1.1)	0	0.0	(3.7)
3	3	3.2	(4.3)	1	3.7	(7.4)
2	8	8.5	(12.8)	2	7.4	(14.8)
1	17	18.1	(30.9)	5	18.5	(33.3)
0	65	69.1	(100.0)	18	66.7	(100.0)

Comments: Irrespective of the method of analysis and data presentation, the concordance in fracture rates between groups is quite striking. The data strongly suggest that there was no treatment-related difference in fractures during the first year of therapy, despite technical difficulties inherent in diagnosis.

The sponsor also performed a reliability assessment, in which 24 patients were randomly selected: eight patients with no new fractures at Month 12, eight with one new fracture, and eight with >1 new fracture. The films were re-read by the panel of radiologists, and κ coefficients were calculated to measure agreement between the first and second readings. Complete descriptions of the methodology and results are provided in the NDA. The results of this analysis applied to the number of new long-bone fractures/patient are given in the following table:

[14] **Comments: The number of significant treatment-by-stratum interactions is most likely due to the relative over-powering of the study. It is important to note that there is no stratum in which the drug was not effective in increasing BMD (i.e., no significant qualitative interaction).**

Reading 1	Reading 2		
	No Fracture	1 Fracture	>1 Fracture
No fracture	6 (25.0%)	2 (8.3%)	0
1 fracture	2 (8.3%)	5 (20.8%)	1 (4.2%)
>1 fracture	0	1 (4.2%)	7 (29.2%)
Kappa Coefficient (95% CI): 0.81 (0.67, 0.96)			
The numbers in parentheses are calculated by dividing by 24. See text for details.			

In this table, at the first reading, eight of the 24 patients had no new fracture at Month 12. When re-read, six were again judged to have no new fracture, two were thought to have one new fracture, and none of the eight was thought to have more than one new fracture. The distributions of new fractures on re-read of the eight with one new fracture and the remaining eight with >1 new fracture are given in the second and third rows. The overall kappa coefficient was 0.81 (0.67, 0.96, 95% CI). Thus the reproducibility of the panel's readings was good but not perfect.

The sponsor also determined whether the fractures were identified at the same anatomical location in both readings and found that for only two of the seven patients with >1 fracture at both readings were the number of fractures equal. For the other five patients, there was a difference of up to three fractures between the two readings. In one patient the panel recorded one fracture in the first reading and six in the second.

The sponsor concludes that the discrepancies apparent in this reliability analysis emphasize the difficulties in reading x-rays of patients who have multiple, severe bone deformities.

A reliability examination of the number of new fractures per bone at seven anatomical sites yielded kappa coefficients ranging from 0.65 to 0.81 (Table 45 of the NDA).

To determine whether the new long-bone fractures seen at the second reading were also seen at the same anatomical location in the first reading, the radiology panel circled the lesion seen in Month 12 digitized images with an electronic marking device. These fracture locations were termed "Regions of Interest" (ROI). An independent radiologist (not on the panel) then compared the ROIs that the panel drew on the first and second readings. The results of this assessment are given in the following table:

Bone	Number of ROIs at First Reading	Number of ROIs at Second Reading	Total Number of ROIs	Number of Matching ROIs (%)
All Long Bones	28	38	45	21 (46.7)
Right Humerus	1	4	4	1 (25.0)
Right Radius	2	2	3	1 (33.3)
Right Ulna	2	2	3	1 (33.3)
Left Humerus	1	3	3	1 (33.3)
Left Radius	2	1	2	1 (50.0)
Left Ulna	1	0	1	0
Right Femur	8	11	13	6 (46.2)
Right Tibia	1	2	2	1 (50.0)
Left Femur	9	11	12	8 (66.7)
Left Tibia	0	1	1	0
Left Fibula	1	1	1	1 (100.0)

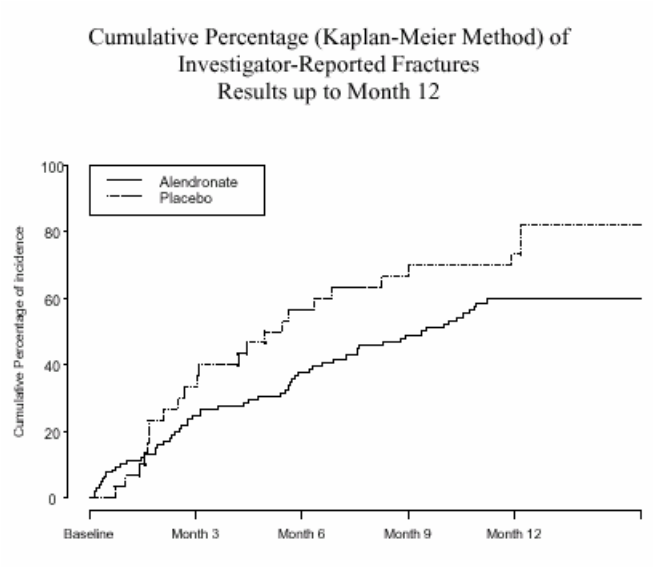
† ROI: Region of Interest; the anatomical location of a new fracture on the Month 12 radiographs compared with baseline.

For all 18 patients with at least one new fracture that was identified by the panel at either read (45 ROIs), the number of matching ROIs for all long bones was only 21 (46.7%). This assessment again demonstrated that the reproducibility of the panel's readings was far from perfect.

B) Investigator-reported fractures

During the double-blind phase, study visits were required every three months. At each visit, the investigators recorded fractures that were reported by the patients or their parents. These fractures were not necessarily confirmed radiologically.

The cumulative incidence of investigator-reported fractures is shown in the following figure:



The cumulative percentages of investigator-reported fractures at Months 3, 6, 9, and 12 and at the end of 12 months of treatment are given in the sponsor's Table 48, part of which is reproduced below:

Month†	Alendronate				Placebo				Treatment Comparison	
	N	n	Cum.%	(95% CI)	N	n	Cum.%	(95% CI)	RD	(95% CI)
Month 3	106	26	24.7	(16.4, 32.9)	30	10	33.3	(16.5, 50.2)	-8.7	(-27.4, 10.1)
Month 6	78	13	37.8	(28.4, 47.1)	20	7	56.7	(38.9, 74.4)	-18.9	(-39.0, 1.1)
Month 9	61	11	49.0	(39.2, 58.8)	13	4	70.0	(53.6, 86.4)	-21.0	(-40.1, -1.9)
Month 12	49	10	59.8	(50.1, 69.5)	9	1	73.3	(57.5, 89.2)	-13.5	(-32.1, 5.0)
Post Month 12	16	0	59.8	(50.1, 69.5)	4	1	82.2	(64.5, 99.9)	-22.4	(-42.6, -2.2)
Overall Between-Treatment Group Comparison: p = 0.058										

N= number of patients likely to report a fracture (excludes those with a previous fracture); n= number of patients with a fracture during the time period; RD= risk difference (a negative RD indicates a lower incidence in ALN, compared to PBO).

At the end of each three-month period, the cumulative percent of patients reporting at least one fracture was numerically lower in ALN, compared to PBO. This is reflected in the consistently negative RDs. The cumulative percentage of patients with at least one investigator-reported fracture up to Month 12 was lower in ALN, compared to PBO (59.8% vs 82.2%, RD (95% CI) = -22.4% (-42.6%, -2.2%). The two treatment groups did not differ significantly in time to first fracture.

The annual rates of investigator-reported fractures (up to Month 12) among the 136 patients with at least one such fracture are presented in Table 49 of the NDA. The mean annual rate of fractures in ALN (1.51 fractures/year) was slightly greater than in PBO (1.33) The treatment difference was not significant (p=0.570). There was no treatment-by-stratum interaction.

The frequency distribution of the number of investigator-reported fractures up to Month 12 is provided in the following table:

Number of Fractures	Alendronate (N=106)			Placebo (N=30)		
	n	%	(Cum.%)	n	%	(Cum.%)
≥5	9	8.5	(8.5)	0	0.0	(0)
4	4	3.8	(12.3)	2	6.7	(6.7)
3	8	7.5	(19.8)	2	6.7	(13.3)
2	18	17.0	(36.8)	7	23.3	(36.7)
1	21	19.8	(56.6)	12	40.0	(76.7)
0	46	43.4	(100.0)	7	23.3	(100.0)

Comments: The sponsor has examined the rates of fracture (both radiologically-confirmed and investigator-reported) in several different ways. Across all analyses, there appears to be no difference in fracture rates between the two treatment groups following twelve months of double-blind therapy. There was, however, a trend in favor of alendronate in investigator-reported fractures. It will be important to analyze data following 24 months of double-blind treatment to see if this treatment difference holds up.

Cortical width

As a pre-specified efficacy endpoint, the sponsor examined the cortical width of the second left metacarpal bone at baseline and Month 12. Using the MITT-LOCF approach, there was a statistically significant ($p \leq 0.001$) mean percent increase from baseline of 10.3% in ALN vs a non-significant increase of 3.1% in PBO. The between-group difference was not significant (p=0.133). The treatment difference in LS means (95% CI) was 8.0% (-2.5%, 18.4%), numerically in favor of ALN.

Cortical width was also measured from iliac crest bone biopsies. The bone biopsies were scheduled to be obtained at baseline and Month 24. At the time of the data cutoff, paired samples were available from 10 patients (seven ALN and three PBO). The median increases from baseline in cortical width in these few specimens were 469 in ALN and 113 in PBO.

Comments: The bone histomorphometry data will be reviewed in their entirety when they are available. These data are of primary concern in the overall analysis of the safety of alendronate in this patient population.

Bone pain

Bone pain histories were recorded at each study visit, either from patient diaries for from reports by the patient or parents (or guardians), if diaries were not kept. The sponsor analyzed the percent of patients with bone pain, the frequency of bone pain, the percent of patients waking at night from bone pain, and the percent of patients with bone pain that interfered with daily activity. The results of each of these analyses are briefly summarized:

The percent of patients in each treatment group who reported bone pain at baseline and at Month 12 did not differ between the two treatment groups, either at baseline or at Month 12. At baseline, 62.7% (64/102) of ALN and 66.7% (20/30) of PBO patients reported bone pain. At Month 12, 46.1% of ALN and 50.0% of PBO reported bone pain. According to the sponsor, the within-group difference in ALN was significant ($p \leq 0.05$), whereas the difference within PBO was not. The between-group differences at Month 12 were not significant (p=0.712). The relative risk (95% CI) was 0.92 (0.61, 1.40). These results were essentially the same using the data-as-observed approach.

The frequency of bone pain, scored as the number of days per week patients reported bone pain, did not differ between the two treatment groups. There were significant mean decreases from baseline in numbers of days of bone pain per week (0.75 in ALN, $p \leq 0.050$; 1.50 in PBO, $p \leq 0.010$). The treatment difference in LS means (95% CI) in percent change from baseline was 0.19 (-0.76, 1.14), which was not statistically significant (p=0.692).

Finally, there was no significant between-group difference in percent of patients reporting waking at night with bone pain. There were significantly fewer patients waking at night with bone pain at Month 12, compared to baseline, in ALN

(17.3% vs 5.1%, p≤0.050). In PBO the within-group difference (21.4% at baseline vs 10.7% at Month 12) was not significant. The RR (95% CI) was 0.47 (0.11, 2.03) in favor of ALN, p=0.299.

Finally, there was no between group difference in the percent of patients who experienced bone pain interfering with daily activity at baseline and at Month 12 (either within- or between-treatment group comparisons).

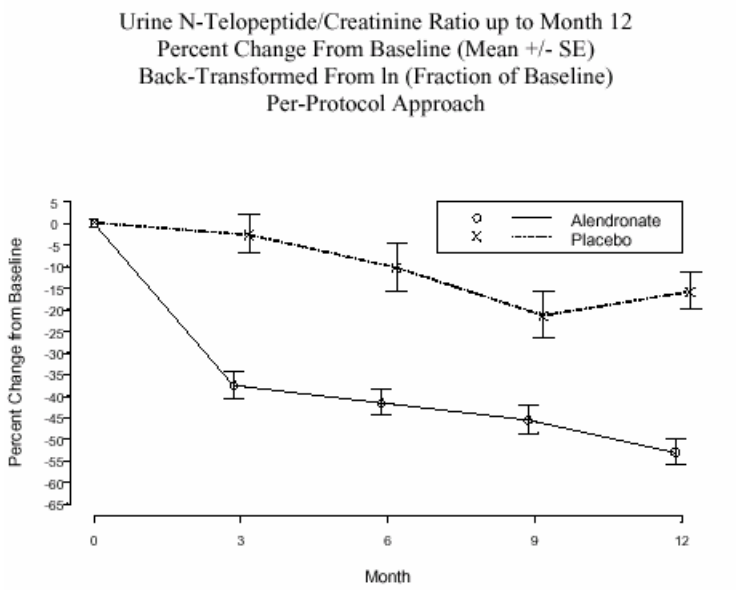
Comments: There were no discernible differences in the occurrence of bone pain, between treatment groups, during the first 12 months of this study.

Biochemical efficacy endpoints

As an exploratory analysis, the sponsor investigated changes in biochemical parameters related to mineral metabolism and bone turnover, in order to acquire more information on the action of alendronate in children with OI. These endpoints were not obtained as surrogates for the action of alendronate on BMD. At baseline and at each study visit, blood was collected for determination of levels of calcium, phosphorus, creatinine, total alkaline phosphatase, iPTH, osteocalcin, and vitamin D metabolites (25-OHD_3, 1,25-$(OH)_2D_3$, and 24,25-$(OH)_2D_3$. In addition, second morning void urine samples were collected at baseline, weekly for the first three months of the double-blind treatment period, and every three months thereafter. Urine samples were analyzed for NTx and Ca/Cr. Baseline and Month 24 urine samples were also analyzed for c-AMP.

Because of the substantial variability inherent in many of these parameters, and because of the large changes from baseline in some of the markers, statistical operations were performed on the log-transformed fraction of baseline [ln(fraction of baseline)]. The results were then back-transformed to produce statistics that summarized the percent change from baseline (the “geometric” percent change). This method is often used to analyze bone marker data. All biochemical analyses in this section used a per-protocol approach. Generally, there were about 64 patients in ALN and about 25 in PBO.

For NTx/Cr, the geometric mean percent changes over time are presented in the following figure:



In ALN, the NTx/Cr levels dropped sharply in the first month and then decreased more slowly during the remainder of the study (data presented in Figure 11 of the NDA). During the first 12 weeks, the NTx/Cr levels were consistently lower in ALN, compared to PBO. At Month 12, the mean decreases from baseline were statistically significant within both treatment groups: 53.2% in ALN ($p \leq 0.001$) and 15.9% in PBO ($p \leq 0.010$). The difference between the treatment groups was significant at 12 months ($p < 0.001$). At 12 weeks, the decline from baseline in ALN, 32.5%, was significant, whereas the decline in PBO, 11.7% was not. The between-group difference was significant ($p = 0.013$)[15].

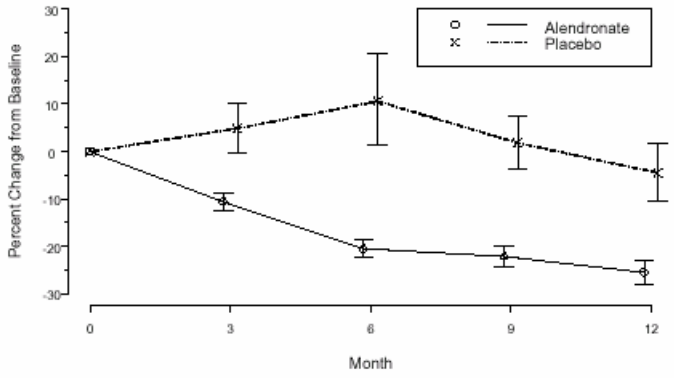
The 12-month data are presented in the following table:

Treatment	N	Means (Observed)		Percent Change From Baseline†	
		Baseline	Month 12	Mean‡	95% CI
Alendronate	67	558.9	290.0	-53.2***	(-58.5, -47.2)
Placebo	27	565.3	473.4	-15.9**	(-24.4, -6.5)
Between-treatment group comparison p-Value				<0.001	

† Back-transformed from ln(fraction of baseline).
‡ Within-treatment test of mean=0: ***:p≤0.001, **:p≤0.010.

The sponsor measured serum alkaline phosphatase and osteocalcin, as indicators of bone formation, at baseline and every subsequent three months throughout the study. Alkaline phosphatase levels decreased by about 20% during the first six months of ALN treatment, with less steep decreases during the next six months. In PBO, the levels remained relatively constant. The mean percent changes in serum alkaline phosphatase up to Month 12 are presented in the next figure:

[15] **Comment**: **As indicated earlier, the description of p-values presented in this review, with the exception of those describing levels of significance for primary outcome variables, are presented in a nominal sense. The 95% CIs are also presented, to give an indication of the distribution of the data.**



In ALN, the decrease from baseline at Month 12, 25.5% was significant ($p \leq 0.001$), whereas the 4.5% decrease in PBO was not. The between-group difference in percent decline from baseline at Month 12 was significant ($p < 0.001$). The data are displayed in the next table:

Treatment	N	Means (Observed)		Percent Change From Baseline†	
		Baseline	Month 12	Mean‡	95% CI
Alendronate	65	267.8	202.1	-25.5***	(-30.3, -20.3)
Placebo	26	286.5	269.7	-4.5	(-16.2, 8.9)
Between-treatment group comparison p-Value				<0.001	

† Back-transformed from ln(fraction of baseline).
‡ Within-treatment test of mean=0: ***:p≤0.001.

For serum osteocalcin, there was a small, non-significant ($p > 0.05$) decrease from baseline at Month 12 in ALN (18.3%) and a smaller decrease in PBO (4.1%). The between-group difference was not significant.

To evaluate the effects of alendronate on mineral homeostasis, the sponsor measured serum levels of calcium, phosphate, 1,25-dihydroxyvitamin D_3, 25-$(OH)D_3$, 24,25$(OH)_2D_3$, and intact PTH, as well as urinary c-AMP and calcium/Cr ratios. As was true for the analyses of bone marker data, most of the remaining analyses used log-transformed data for statistical operations. The results were then back-transformed and expressed as geometric means.

Serum calcium levels were determined at baseline and every three months thereafter. Over the twelve months of the trial, geometric mean serum calcium levels remained stable in ALN (decrease of –0.9%, 95% CI –1.9, 0.1), but increased slightly in PBO (+1.5%, 95% CI –0.4, 3.4). The within-group changes from baseline were not significant, but the p-value on the difference between the groups was 0.028). The data are described in more detail in the NDA.

Serum phosphate levels remained stable in PBO. In ALN, levels of phosphate declined during the first three months of treatment and then leveled off for the remainder of the twelve-month period. By Month 12, the geometric mean change

in ALN was –9.6% (-13.1, -6.0, p≤0.001). The change in PBO was –0.2% (-5.0, 4.9, ns). The p-value on the between-group comparison was 0.003.

Urine Ca/Cr was measured at baseline, once weekly for the first three months, and every three months thereafter. In this assessment, the sponsor analyzed the median percent changes in Ca/Cr ratios. In PBO, levels of Ca/Cr remained stable over the 12-month period. In ALN, the levels decreased during the first two weeks of double-blind treatment and then remained stable for the remainder of the study. The initial median decline was about 50% of baseline. By Month 12, the median percent change from baseline was –41.5 in ALN (-62.6, -19.6) in ALN, compared to –9.8% (-50.0, 20.6) in PBO. The p-value (rank-based test) on the between-group difference was 0.268.

1,25-dihydroxyvitamin D (calcitriol) was measured at baseline and every three months. In ALN the levels of calcitriol increased during the first three-month period and then remained stable. In PBO, there was essentially no change from baseline to Month 12. The geometric mean increase at 12 months in ALN was 26.4% (13.4, 40.9, p≤0.001 for within-group change from baseline), compared to a non-significant decline in PBO of –12.0% (-28.3, 8.1). The between-group difference in percent change from baseline was significant (p<0.001).

The sponsor also presents an analysis in changes in serum levels of 25-OHD_3 and 24,25-$(OH)_2D_3$. There were no significant changes in mean levels of these vitamin D metabolites from baseline to Month 12. There were no significant differences between the two treatment groups in percent changes from baseline at Month 12.

Serum iPTH levels are also presented as geometric mean percent changes, back-transformed from ln (fraction of baseline). In ALN, there was an increase from baseline, about 19%, that was apparent within three months of treatment. At Month 12, the percent change from baseline was 19.1% (9.5, 29.4, p≤0.001 for within-group change from baseline). In PBO, there was an increase of 3.4% (-11.0, 20.0). The between-group difference was not significant (p=0.105).

Urinary c-AMP values were measured at baseline and Month 24 only. Consequently, data are not yet available.

Serum creatinine levels increased in both treatment groups, by about 20% from baseline. The levels and time courses of creatinine values were essentially the same in the two groups. For ALN, the mean percent change from baseline was 17.5 (8.0, 27.9); for PBO, the values were 21.0 (6.9, 37.0).

Comments: These exploratory analyses demonstrate some of the expected effects of alendronate in this high turnover state. Of greatest importance, biochemical markers of bone turnover and formation, NTx and alkaline phosphatase, were suppressed substantially by alendronate therapy. Serum osteocalcin, another marker of bone formation was suppressed by alendronate, but only modestly. Serum calcium levels did not change in either treatment group; however, there was a decline (about 10%) in serum

phosphate levels in ALN, with no change in PBO. Both iPTH and 1,25-dihydroxyvitamin D levels increased in ALN, but not in PBO. There was a numerically greater decline in urinary Ca/Cr in ALN, compared to PBO (there were no treatment-related changes in serum creatinine levels, although both groups demonstrated mean increases of about 19% during the study). Other vitamin D metabolites did not differ appreciably between the two groups. Taken together, these changes are in accord with the small increases in PTH that are expected to occur in response to the inhibition of bone resorption that is associated with alendronate therapy.

Vertebral height:

The sponsor attempted to measure treatment-related changes in vertebral height. Baseline and Month 12 radiographs were digitized and (b) (4) attempted to identify six landmarks on each of 14 vertebrae (L1-5 and T4-12). These permitted three height measurements/vertebral body: anterior, posterior, and midline. Unfortunately, a large proportion of baseline and Month 12 measurements were unable to be included in the analysis, mainly due to the high prevalence of baseline vertebral deformities, fractures, and extremely low BMD. The analysis excluded about 35% of vertebral height measurements in the anterior, posterior, and midline axes for these reasons and an additional 15-20% due to lack of assessable baseline and Month 12 pairs. Thus the final analysis of vertebral height included about 55% of the total number of possible measurements[16].

For the midline vertebral height, there were significant mean percent increases from baseline of 8.2% in ALN ($p<0.001$) and 16.9% in PBO ($p<0.010$) at Month 12. The between-group differences were not significant ($p=0.512$). The treatment difference [LS means (95% CI)] in percent change from baseline was 3.4% (-6.9%, 13.7%) in favor of alendronate.

Similar results were obtained using anterior and posterior vertebral heights (data in NDA, not presented here).

Pediatric evaluation of disability inventory (PEDI)

This disability inventory has not been validated in pediatric patients with OI and was an exploratory endpoint in the trial. The evaluation was conducted by an occupational therapist at baseline and every six months thereafter.

The following six domains were tested as part of this evaluation:
- Self-care—Functional skills
- Mobility—Functional skills
- Social Function—Functional skills
- Self-care—Caregiver Assistance
- Mobility—Caregiver Assistance

[16] There were three height determinations in each of 14 vertebrae = 42 assessments/patient X 125 patients = 5124 measurements, or 1708 measurements for each of the three axes.

- Social Function—Caregiver Assistance (this domain was optional)

The sponsor presents the results of the analysis of change from baseline at Month 12 for the first, second, fourth, and fifth domains. In this analysis, both MITT-LOCF and data-as-observed scaled score results of all post-baseline time points are presented. For all four scores, there were small but significant increases from baseline in ALN, whereas there were small but non-significant increases in PBO. The treatment-group differences were not significant at Month 12. Details of this exploratory analysis are presented in the NDA and are not presented here.

Similarly, there were improvements in parental assessment of the patient's physical activity (assessed on a five-point scale at baseline and at every visit) in ALN, but not in PBO. Again, the treatment-group difference was not significant at Month 12.

Grip strength was assessed using a hand dynamometer at baseline and every six months during the double-blind phase of the study. There were comparable increases grip strength in the dominant hand in ALN and PBO from baseline to Month 12. Both within-group changes were significantly ($p \leq 0.001$) different from baseline. The between-group difference was not significant.

Femoral neck angle was measured at baseline and Month 12 in 60 patients. There were no significant changes in either treatment group, and because of the work schedule of the radiology panel, the PSC has decided to abandon this part of the project.

Comments: This concludes the sponsor's description of efficacy results at Month 12. It is clear that twelve months of treatment with alendronate, 5mg or 10 mg daily, is associated with a dramatic increase in lumbar spine BMD, relative to placebo in pediatric patients with OI. The magnitude of the change strongly suggests the presence of a high turnover state in the majority of patients. The changes in bone marker data, conducted as an exploratory analysis of the pharmacodynamics of alendronate in this patient population, are consistent with this interpretation. These changes are also in accord with the known action of alendronate on bone resorption. Other changes in indices of mineral metabolism were also consistent with this effect. Further analyses disclosed no subgroup, including weight stratum, in which alendronate was not effective in increasing BMD.

Despite the dramatic changes in BMD, there was no evidence of clinical benefit, particularly on the risk of fractures. The clear lack of effect on fractures (positive or negative) most likely led the DSMB to permit continuation of the double-blind phase of the study up to Month 24.

These results are somewhat surprising, given the extraordinary large increase in BMD. However, the pathophysiology of OI differs considerably from that of post-menopausal osteoporosis. It is entirely possible that, in

the former condition, the contribution of poor matrix to bone fragility cannot be overcome by increasing bone mineral.

The sponsor's contention that the lack of fracture benefit is due to underlying bone deformity is not entirely convincing, particularly in view of the fairly consistent concordance of results in both treatment groups across a variety of numerical analyses (fracture rate, number of fractures per patient, number of fractures per bone, cumulative occurrence of fractures, etc.). In addition, there was no treatment-group difference in the incidence of investigator-reported fractures (which are not dependent on radiological confirmation), although there appears to have been a trend in favor of alendronate in the cumulative incidence of fractures and of proportions of patients with at least one new fracture.

The sponsor's assertion that the trial was not powered to detect a difference in fracture rate is also unconvincing. The fracture rate is very high in this population, particularly when expressed as fracture incidence instead of proportion of patients with at least one fracture. One would expect to find at least a trend in favor of alendronate, if there were an underlying treatment effect. Understandably, a formal power analysis based on known rates, unknown methodology, and unknown standard deviations was not feasible.

This trial is ongoing, and final judgment regarding the clinical efficacy of alendronate in pediatric patients with OI will have to await analysis of the 24-month fracture data.

VIII Safety outcomes

A complete analysis of clinical and laboratory adverse experiences in included in the submission. In accord with the Written Request, the submission contains summaries and descriptions of AEs reported up to Month 12. This includes all safety data for all randomized patients from the start of double-blind treatment up to and including the Month 12 study visit (or up to study day 365, whichever came later). The sponsor also includes all safety data obtained after Month 12. These are designated "Results up to Month 24." All adverse experiences were recorded, analyzed, and presented according to routine procedures. In addition, the sponsor performed separate analyses of gastrointestinal AEs, bone histomorphometry, and fracture healing rates. This review will concentrate on data provided for the period up to Month 12. Important aspects of the results up to Month 24 (such as analyses of deaths, serious AEs, and special studies) will also be included.

Extent of exposure:

This study randomized 109 patients to ALN and 30 to PBO. Of these, 89 (81.7%) of ALN and 29 (96.7%) of PBO took at least 12 months of study medication (defined as at least 275 days) during the period up to Month 12. The mean total duration of exposure in ALN was 317.7 days (range, 40 to 444 days) and, in PBO, 348.5 days (range, 270 to 378 days). The median exposure time was the same in both groups (356 days).

The following table presents the number of patients taking study medication, by dose and time point:

	Month 3	Month 6	Month 9	Month 12	Post Month 12	Total Number of Patients	Day Range	Average No. of Days
Alendronate (both strata combined[1])	6	7	7	71	18	109	40 to 444	317.7
Placebo (both strata combined[1])	0	0	1	25	4	30	270 to 378	348.5
Alendronate 5 mg	3	6	6	57	12	84	40 to 435	323.3
Alendronate 10 mg	3	1	1	14	6	25	51 to 444	298.7

For safety data past 12 months (i.e., "Results up to 24 Months"), the median exposure times were 545 days in ALN (range 40-751) and 612 days in PBO (range 295-732).

Clinical adverse experiences were reported in 85 patients (78.0%) in ALN and in 27 patients (90.0%) in PBO ($p>0.050$ for between-group difference in total clinical AEs). Serious AEs occurred in four patients (3.7%) in ALN and in two patients (6.7%) in PBO. Fractures, which are usually reported as serious AEs, were analyzed as a secondary efficacy endpoint and have been reviewed (above). No serious AE resulted in discontinuation from the study. The sponsor states that none of the serious AEs was considered "drug related"[17] by the investigator. No patient died during the study.

There were no detectable treatment-group differences in the number or percent of patients with one or more AEs, with no AEs, serious AEs, "drug-related " AEs, or serious "drug-related" AEs. There were no treatment-group differences in the number or percent of patients who discontinued due to AEs, serious AEs, or "drug-related" AEs (serious or not). There were no deaths in either group. The data are displayed in table 79 of the NDA.

Clinical AEs are also displayed by stratum in Table 80 of the NDA. There were no overt differences in incidence of clinical AEs among the four groups (ALN 5, ALN 10, PBO 5, PBO 10) that would signal particular vulnerability to alendronate (e.g., small children receiving 5 mg). The numbers of patients in each group were small, however.

The differences in percent of patients (ALN vs PBO) with clinical AEs, by body system, along with 95% CIs, are displayed in Table 81 of the NDA. The

[17] **Comments: The designation "drug-related" is determined by the investigator and is not a completely objective or reliable descriptor.**

differences were small across all 13 body systems, ranging from –4.6 to + 11.7 (a negative number is in favor of ALN) in no treatment-group comparison did the 95% CI fail to include zero.

The sponsor conducted a similar analysis of clinical AEs by body system for each of the four treatment-by-stratum groups. The data, summarized in Table 82 of the NDA, show that the incidences of clinical AEs by body system were similar in ALN 5 mg vs PBO 5 mg, and in ALN 10 mg vs PBO 10 mg. In particular, there were no overt differences, across the four treatment-group strata, in GI AEs, although again, the numbers of patients in each group were small.
The most common clinical AEs for ALN and PBO, and their incidence rates, respectively, were: upper respiratory infection (19.3% and 30.0%), headache (20.2% and 16.7%), and influenza-like disease (11.9% and 13.3%). The most common digestive system–related AEs in ALN and PBO, respectively, were: vomiting (15.6% and 6.7%), epigastric discomfort (1.8% and 16.7%), nausea (9.2% and 10.0%), and gastric disorder (7.3% and 10.0%).

Table 83 in the NDA summarizes specific clinical AEs as treatment-group differences in percentages of patients, with 95% CIs on the differences. A review of this table, which describes 125 reported specific clinical AEs, grouped by body system, showed no clear treatment-related differences in incidence rates over the 12 months of the study. In general, the size of the differences was small (usually < 5% in either direction), and nearly every 95% confidence interval around the difference included zero.

In particular, a review of the 20 AEs recorded under Digestive System yielded the same results, with small treatment-related differences, usually less than 5%. There was no increase in the incidence of upper GI AEs. Further details on upper GI adverse events are presented under special safety studies, below. Of added recent concern, there was no obvious increase in the number or percent of ocular symptoms. There were two reports of conjunctivitis in ALN, vs none in PBO. There were no reports of uveitis, episcleritis, or other inflammatory eye disorders in either treatment group during the initial twelve months. There was no overt increase in musculoskeletal AEs, including joint swelling or myalgia. There were no reports of peripheral edema. A review of specific symptoms by stratum also revealed no treatment-by-stratum interaction in this analysis (details in Table 84 of the NDA). Again, there were fewer patients in the higher stratum, limiting the utility of this analysis.

The sponsor also presents an analysis of clinical AEs that were “determined by the investigator to be drug-related.” These are detailed in the NDA (Table 85). The most commonly reported AEs in this category were in the digestive body system: 14 (12.8%) in ALN and 8 (26.7%) in PBO. Three patients (2.8%) in ALN and three (10.0%) in PBO had “drug-related” nausea and one (0.9%) ALN and three (10.0%) PBO patients experienced “drug-related” epigastric discomfort. The incidence of drug-related AEs in the other body systems was similar in ALN and PBO.

Serious clinical AEs:

Six patients in the entire study population experienced at least one serious AE (excluding fractures) during the 12-month double-blind treatment period: Four in ALN (3.7%) and two in PBO (6.7%).
Deaths: There were no deaths during the study (either in the first 12-month period or in the data reported for the 24-month period).

Patient narratives for all six serious clinical AEs are presented in the NDA. There were four in the ALN 5 mg group, one in PBO 5 mg, and one in PBO 10 mg. In the ALN 5 mg, the AEs were: nerve palsy, two patients with bone fixation device complications, one patient with pneumonia, and pleural effusion. In the PBO 5 mg group, there was one patient with asthma, pneumonia, and a laceration. In PBO 10 mg, there was one patient with a torn ligament. None of these AEs resulted in discontinuation from the study and none was judged by the investigator to be related to study drug.

Serious clinical AEs occurring up to Month 24:

The sponsor provides a listing of all serious clinical AEs occurring after Month 12 and up to Month 24. There were four such patients in ALN and none in PBO. These AEs were: skull deformity, dehydration, nerve palsy, and constipation. None were considered by the investigators to be related to study drug.

Patients who discontinued up to Month 12 due to Clinical AEs:

Four patients (2.9%) in ALN and three (2.8%) in PBO discontinued in the period up to Month 12 due to a clinical AE. The specific AEs are presented in the NDA. In ALN 5 mg, the AEs were vomiting (judged definitely related to study drug) and abdominal pain (possibly related). In PBO 5 mg, the cause was abdominal pain (judged probably related). In ALN 10 mg the cause was agitation (judged probably not related).

Comments: I have reviewed the case histories of all patients with serious AEs. The aspiration pneumonia (one patient) was acquired during the placebo run-in period. The other ten AEs occurred during the double-blind treatment period, up to Month 24. Seven of these patients received alendronate 5 mg., two received placebo, and one received alendronate 10 mg.

For the seven patients receiving alendronate 5 mg: In one patient, radial nerve palsy was the immediate result of elective surgery that was intended to correct a right forearm deformity. One patient had surgery to correct protruding hardware. One patient required surgery to correct a protruding lateral rod that had been placed for treatment of a prior hip fracture. One patient, a 12-year-old girl had pneumonia with a pleural effusion about one month after starting alendronate 5 mg. The patient was treated with i.v. antibiotics and recovered. One patient had sciatic nerve palsy at baseline (felt to be a complication of surgery to correct bowing of the tibia). During the trial, the patient underwent further tibial surgery and the palsy

persisted and had not recovered by the time of the final report. The reporting physician thought that the persistent palsy was unrelated to study drug. One patient had life-threatening dehydration after a tonsillectomy. Apparently, the study drug (alendronate 5 mg) had been stopped one day prior to the operation, but the dehydration was due to vomiting and dysphagia. The investigator thought that the dehydration was not related to study drug. I do not have enough clinical details to offer an opinion, except that it is conceivable that the vomiting and dysphagia were in fact related to alendronate. The patient recovered, following treatment with i.v. fluids. The seventh patient in this treatment group had moderate constipation, which began nearly two years after beginning double-blind therapy. Concomitant therapy included hydrocodone. The patient was treated with glycerin suppositories and mineral oil, but began vomiting and developed a fever the following day. Over the next few days, the patient experienced more vomiting, with diarrhea and dehydration. He was treated with i.v. fluids and recovered. The investigator thought that the constipation and dehydration were probably not related to study drug therapy. In my opinion, the constipation was probably not related, but it is possible that the vomiting and subsequent dehydration were.

One patient receiving alendronate 10 mg had a serious AE, occurring about 18 months after starting double-blind study drug. The patient developed numbness and weakness on the right side of the body, which was diagnosed as a basilar invagination with possible syrinx. This is a developmental abnormality of the skull. The syrinx is formed secondarily. The patient required surgery to repair the basilar invagination. The investigator thought that the AE was unrelated to study drug.

Two patients had serious AEs while receiving placebo. One had an anterior cruciate ligament tear in her left knee for which she underwent corrective surgery. During the procedure, she had an intraoperative fracture of the tibia. She recovered fully from the anterior cruciate ligament tear. The reporting physician judged the ligament tear to be unrelated to study drug. Finally, one patient had asthma and pneumonia, requiring hospitalization. The patient was hospitalized, treated, and recovered. Following discharge, he fell on his left arm and required surgery to repair the injured hardware that had been placed in the past. These AEs were thought not to be related to study drug.

As of the cutoff date, no patient died in this study. In the opinion of the investigators, no patient has experienced a serious adverse experience that was related to study drug. In my opinion, no patient had a serious AE that was definitely or probably related to study drug. It is possible, however, that alendronate contributed to the vomiting experienced by two of the patients.

Serious laboratory AEs: There was one serious laboratory AE reported in the study. A nine-year-old girl developed leukopenia that was detected at her three-month visit (her baseline CBC was normal). At three months she had a normal

hemoglobin level and platelet count, but her WBC was 3900/mm^3, with an absolute neutrophil count of 1182. At that time she had a flu-like illness.. Three months later, her CBC was essentially the same. Two weeks after that, her WBC was 4000, with a normal absolute neutrophil count of 2160. However, not known to the investigator, she had stopped study medication two days before this. Two weeks after that, her WBC was 5100, with an ANC of 2601. However, two months later, while the patient was still off study drug, her ANC was noted to be low (between 1200 and 1300). The investigator was reluctant to restart study medication until receipt of a consult from a pediatric hematologist. The consultant thought that an underlying hematologic explanation was unlikely. A work-up has failed to disclose the cause of the leukopenia. The consultant recommended monthly follow-up hematology visits. The patient has not received further study medication, and additional details are not available.

The sponsor also conducted analyses of adverse experiences that are of special interest, because of known AEs associated with alendronate, and owing to the unique nature of the treatment population.

Upper GI AEs: Upper GI adverse events were included as an additional study because abdominal pain and esophageal injury (esophagitis, ulceration, bleeding, and even perforation) have been reported in association with alendronate use in postmenopausal women. In addition, cases of gastric and duodenal ulceration have been reported. Oral ulceration has also been found in association with alendronate.

Comments: Alendronate has the potential to irritate any portion of the GI tract, with the greatest number of occurrences involving the esophagus. It is likely that many of the post-marketing GI adverse events occurred in patients who did not follow instructions carefully. Related to this, many GI AEs have occurred in patients who were very old, infirm, bedridden, and who were not reasonable candidates for anti-resorptive therapy. We have no reliable data regarding the GI safety of alendronate in the pediatric population. Further comments on the general applicability of GI safety findings in controlled studies of Fosamax appear at the conclusion of this section.

In general, there were no treatment-group differences in the per cent of patients with clinical upper GI AEs, which occurred in 36 ALN patients (33.3%) and 12 in PBO (40.0%). Similarly, there were no differences in “drug-related” (i.e., considered by the investigator to be possibly, probably, or definitely related) upper GI AEs between the groups [these occurred in 18 ALN patients (16.5%) and 9 in PBO (30.0%)]. Two patients in ALN (1.8%) and one in PBO (3.3%) discontinued because of a clinical upper GI AE, up to Month 12. There were no serious upper GI AEs in either treatment group.

A summary of clinical upper GI AEs (up to Month 12), with differences in percentages (with 95% CIs) between treatment groups, is presented in Table 88 of the NDA, reproduced below:

	Comparison	Difference in Percentages		Alendronate (N=109)	Placebo (N=30)
		Estimated	95% CI	n (%)	n (%)
With one or more adverse experiences	Alendronate vs. Placebo	-7.0	(-26.4, 11.0)	36 (33.0)	12 (40.0)
With no adverse experience	Alendronate vs. Placebo	7.0	(-11.0, 26.4)	73 (67.0)	18 (60.0)
With drug-related adverse experiences[4]	Alendronate vs. Placebo	-13.5	(-32.3, 2.1)	18 (16.5)	9 (30.0)
With serious adverse experiences	Alendronate vs. Placebo	0.0	(-11.4, 3.4)	0	0
With serious drug-related adverse experiences	Alendronate vs. Placebo	0.0	(-11.4, 3.4)	0	0
Who died	Alendronate vs. Placebo	0.0	(-11.4, 3.4)	0	0
Discontinued due to adverse experiences	Alendronate vs. Placebo	-1.5	(-14.9, 3.9)	2 (1.8)	1 (3.3)
Discontinued due to drug-related adverse experiences	Alendronate vs. Placebo	-1.5	(-14.9, 3.9)	2 (1.8)	1 (3.3)
Discontinued due to serious adverse experiences	Alendronate vs. Placebo	0.0	(-11.4, 3.4)	0	0
Discontinued due to serious drug-related adverse experiences	Alendronate vs. Placebo	0.0	(-11.4, 3.4)	0	0

An identical table, with results up to Month 24, is presented in Appendix 4.2.128 of the NDA. The data are reproduced below (negative percent differences are numerically in favor of alendronate):

Number (%) of patients:	Comparison	Difference in Percentages		Alendronate (N=109)	Placebo (N=30)
		Estimated	95% CI	n (%)	n (%)
With one or more adverse experiences	Alendronate vs Placebo	0.1	(-19.3, 19.0)	51 (46.8)	14 (46.7)
With no adverse experience	Alendronate vs Placebo	-0.1	(-19.0, 19.3)	58 (53.2)	16 (53.3)
With drug-related adverse experiences[a]	Alendronate vs Placebo	-11.9	(-31.1, 5.4)	27 (24.8)	11 (36.7)
With serious adverse experiences	Alendronate vs Placebo	0.0	(-11.4, 3.4)	0	0
With serious drug-related adverse experiences	Alendronate vs Placebo	0.0	(-11.4, 3.4)	0	0
Who died	Alendronate vs Placebo	0.0	(-11.4, 3.4)	0	0
Discontinued due to adverse experiences	Alendronate vs Placebo	-1.5	(-14.9, 3.9)	2 (1.8)	1 (3.3)
Discontinued due to drug-related adverse experiences	Alendronate vs Placebo	-1.5	(-14.9, 3.9)	2 (1.8)	1 (3.3)
Discontinued due to serious adverse experiences	Alendronate vs Placebo	0.0	(-11.4, 3.4)	0	0
Discontinued due to serious drug-related adverse experiences	Alendronate vs Placebo	0.0	(-11.4, 3.4)	0	0

Overall, the data demonstrate that the small group differences are stable when exposure increases.

The sponsor also presents summaries of clinical upper GI AEs in the four treatment-by-stratum subgroups. These AEs occurred in 34.5%, 45.8%, 28.0%, and 16.7% of patients in ALN 5 mg, PBO 5 mg, ALN 10 mg, and PBO 10 mg, respectively. Details of treatment-by-stratum upper GI AEs are presented in Table 89 of the NDA. A similar analysis of effects up to Month 24, with essentially the same results, is presented in Appendix table 4.2.129.

The incidences of specific types of upper GI AEs up to Month 12 are presented in Table 90, reproduced below. There were no patients with clinically apparent gastric ulcers or esophagitis. Gastritis occurred in one patient in ALN and none in PBO. More patients experienced vomiting in ALN (15.6%), compared to PBO (6.7%).

	Comparison	Difference in Percentages		Alendronate (N=109)		Placebo (N=30)	
		Estimate	95% CI	n	(%)	n	(%)
Patients With One or More Adverse Experiences	Alendronate vs. Placebo	-7.0	(-26.4, 11.0)	36	(33.0)	12	(40.0)
Patients With no Adverse Experience	Alendronate vs. Placebo	7.0	(-11.0, 26.4)	73	(67.0)	18	(60.0)
Body As A Whole/Site Unspecified	**Alendronate vs. Placebo**	**-0.8**	**(-17.0, 8.7)**	**10**	**(9.2)**	**3**	**(10.0)**
Abdominal Distention	Alendronate vs. Placebo	-3.3	(-16.7, 1.0)	0		1	(3.3)
Abdominal Pain	Alendronate vs. Placebo	-0.8	(-17.0, 8.7)	10	(9.2)	3	(10.0)
Digestive System	**Alendronate vs. Placebo**	**-4.9**	**(-24.3, 11.9)**	**31**	**(28.4)**	**10**	**(33.3)**
Acid Reflux	Alendronate vs. Placebo	-3.3	(-16.7, 1.0)	0		1	(3.3)
Dyspepsia	Alendronate vs. Placebo	-3.3	(-16.7, 1.0)	0		1	(3.3)
Epigastric Discomfort	Alendronate vs. Placebo	-14.8	(-31.8, -4.4)	2	(1.8)	5	(16.7)
Esophagalgia	Alendronate vs. Placebo	0.9	(-10.5, 5.0)	1	(0.9)	0	
Gastric Disorder	Alendronate vs. Placebo	-2.7	(-18.7, 6.5)	8	(7.3)	3	(10.0)
Gastritis	Alendronate vs. Placebo	0.9	(-10.5, 5.0)	1	(0.9)	0	
Gastroenteritis	Alendronate vs. Placebo	1.8	(-9.6, 6.4)	2	(1.8)	0	
Gastroesophageal Reflux Disease	Alendronate vs. Placebo	0.9	(-10.5, 5.0)	1	(0.9)	0	

	Comparison	Difference in Percentages		Alendronate (N=109)		Placebo (N=30)	
		Estimate	95% CI	n	(%)	n	(%)
Digestive System (Cont.)	**Alendronate vs. Placebo**	**-4.9**	**(-24.3, 11.9)**	**31**	**(28.4)**	**10**	**(33.3)**
Gastrointestinal Disorder	Alendronate vs. Placebo	-3.3	(-16.7, 1.0)	0		1	(3.3)
Gastrointestinal Distress	Alendronate vs. Placebo	0.9	(-10.5, 5.0)	1	(0.9)	0	
Heartburn	Alendronate vs. Placebo	2.8	(-8.7, 7.8)	3	(2.8)	0	
Nausea	Alendronate vs. Placebo	-0.8	(-17.0, 8.7)	10	(9.2)	3	(10.0)
Vomiting	Alendronate vs. Placebo	8.9	(-6.8, 18.2)	17	(15.6)	2	(6.7)

The types and incidences of upper GI AEs up to Month 24 are presented in Appendix 4.2.136 of the NDA. The results were similar to the 12-month data. There were no additional patients with gastritis and no clinical ulcers or esophagitis reported in data up to Month 24. The group difference in proportions of patients with vomiting increased slightly, however (to 22.9% of patients in ALN vs 10.1% in PBO).

In considering the relevance of special GI safety assessments, it should be noted that no controlled Fosamax study has been able to demonstrate treatment group-related differences in GI AEs, despite the fact that we know, from extensive post-marketing experience, that these AEs are associated with alendronate therapy[18]. The most that one can conclude from the present analysis is that there is no obvious safety "signal" regarding the use of alendronate in this population.

Other special safety studies

Ocular adverse experiences: As of Month 12, one patient (ALN 5 mg) had amblyopia, one patient each in ALN 5 mg and ALN 10 mg had conjunctivitis, one (ALN 5 mg) had a hordeolum and one (PBO 10 mg) had increased lacrimation.

Acute phase response:

Several adult patients receiving alendronate have reported an acute phase-like response, occurring within 24-48 hours of initiating therapy. This reaction is

[18] **See my earlier reviews of Fosamax efficacy supplements for more complete discussion of the relationship of clinical trial subjects to the wider marketed population.**

characterized by “flu-like” symptoms, with fever and myalgias. This syndrome resolves promptly.

In the present study, no fevers were reported in any patient upon initiation of study medication. The earliest appearance of fever was Day 6 in one patient receiving alendronate 5 mg. The fever lasted three days and resolved. Three patients, all receiving alendronate 5 mg, reported “influenza symptoms” during the first seven days after initiating study medication (Days 1,4, and 6). All three patients recovered within three weeks. No patient in PBO reported “influenza symptoms” within the first seven days of initiating treatment. “Myalgia” was not reported by any patient during the first seven days of treatment.

Laboratory AEs

Laboratory data are summarized for 133 of the 139 patients who entered the study, because six patients discontinued before any post-baseline laboratory values were obtained.

Only two patients (1.5% of the trial population) had laboratory adverse experiences (one anemia and one leukopenia), both in ALN 5 mg. Both adverse events were considered to be drug-related by the investigator. One of these patients discontinued because of this AE. This was the nine-year-old girl with leukopenia, described above[19]. No serious laboratory AEs occurred after Month 12 (data included in “up to Month 24”).

Other laboratory safety analyses include a presentation of laboratory values over time and changes exceeding pre-defined limits. The former analysis, presented in tables 4.2.143-4.2.158 in the NDA Appendix, uses the MITT LOCF approach to tabulate trends in mean values in each treatment group.

Comment: This analysis, which included data up to Month 24, disclosed no obvious safety signals. However, this type of analysis, in which means of continuous variables are presented, can exclude important outliers.

The sponsor established predefined limits and limits of change for laboratory safety analyses. In ALN and PBO, 4.2% and 0.0% of patients, respectively, had decreases that were at least 30% and values less than the lower limit of normal for serum phosphate. In addition, 19.8% and 16.7% of patients in ALN and PBO, respectively, had increases in serum creatinine $\geq$ 50% of baseline. Up to Month 12, there were no significant between-group differences in percentage of patients with any laboratory values outside the pre-defined limits. The data are summarized in Table 95 of the NDA, and data up to Month 24 are provided in 4.2.159 of the NDA.

Comments: Possibly related to the case of neutropenia, described above, there were slightly more patients in ALN with low WBC counts and with low

[19] **On page 258, this particular adverse event is described as “serious” under Clinical AEs, but (pg. 276 and Table 94) as “not serious” under Laboratory Adverse Events. I consider this event to be serious.**

neutrophil counts, compared with PBO. The sponsor states that none of the treatment group comparisons was "significant" because the p-value was > 0.05. In my opinion, this is a misuse of the p-value. When applied to multiple comparisons in a safety screen, the use of a p-value with no prior hypothesis is useful only for suggesting that a signal may be present. If this is the purpose, then the stringency of the test should probably be reduced, say to 0.10, if only to increase the level of alertness in examining future safety data.

In fact, perusal of the data up to Month 24 (4.2.159) shows that the percent of patients with a decrease in WBC > 20% and value < LLN was 17/94 (18.1%) in ALN and 2/27 (7.4%) in PBO. The corresponding values for neutrophil counts up to Month 24 were 11/62 (17.7%) in ALN and 1/16 (6.3%) in PBO. Of course, other values changed during this additional observational interval (e.g., there was an increase in proportion of patients with an elevation in WBC in ALN). However, the possibility of drug-associated neutropenia should be investigated further, if alendronate is to be approved for pediatric patients. Neutropenia is not known to occur with increased frequency in adults using alendronate. Part of the Table 4.2.159, summarizing data up to Month 24 for WBC and for neutrophil counts is reproduced below:

WBC COUNT					
Decrease ≥ 20% and Value <LLN	Alendronate	17/ 94 (18.1)	Alendronate vs Placebo	10.7	(-6.5, 21.1)
	Placebo	2/ 27 (7.4)			
Increase ≥ 20% and Value >ULN	Alendronate	7/ 94 (7.4)	Alendronate vs Placebo	7.4	(-5.6, 14.6)
	Placebo	0/ 27			
Value<LLN	Alendronate	33/ 102 (32.4)	Alendronate vs Placebo	12.4	(-6.8, 26.6)
	Placebo	6/ 30 (20.0)			
NEUTROPHIL COUNT					
Decrease ≥ 20% and Value<LLN	Alendronate	11/ 62 (17.7)	Alendronate vs Placebo	11.5	(-11.8, 23.9)
	Placebo	1/ 16 (6.3)			
Increase ≥ 50% and Value>ULN	Alendronate	4/ 62 (6.5)	Alendronate vs Placebo	0.2	(-22.2, 10.6)
	Placebo	1/ 16 (6.3)			

Vital signs and other related safety observations:

The study protocol did not require recording of heart rate and blood pressure on case report forms. Clinical safety parameters included BMI, weight, standing and sitting height, and arm span. These were measured at baseline and every three months during the double-blind phase of the study. The sponsor presents a detailed analysis of changes in these parameters, using both the MITT-LOCF data-as-observed approaches. Results are presented both for data up to Month 12 and data up to Month 24.

The BMI z-score increased from baseline to Month 12 in ALN but not in PBO. The increase in ALN was 0.25 BMI z-score units, vs a decline of 0.11 units in PBO. The within-group change was significant in ALN ($p \leq 0.01$) but not in PBO. The between-group difference was not significant. The sponsor also presents the proportion of patients who attained thresholds for change from baseline in BMI z-

score at Month 12. A numerically greater proportion of patients increased BMI z-score in ALN than in PBO (details in Table 97 of the submission).

Similar results were obtained when the change from baseline in BMI was analyzed. The mean baseline BMI in ALN was 20.74 kg/m^2 and increased to 21.99 kg/m^2 during the first 12 months (95% CI 0.79, 1.71, p ≤0.001). In PBO, the baseline BMI was 20.07 and increased to 20.52 (-0.68, 1.59).

Data up to Month 24 are presented in Appendix 4.2.161 of the NDA. The above pattern continued through Month 18, but by Month 24 the BMI z-score had increased somewhat in PBO and, depending on whether the MITT-LOCF or the data-as-observed approach was used, there was little or no difference between the groups at this final time point.

The mean weight z-scores remained approximately stable for the first 12 months in both treatment groups. However, this pediatric population is growing; consequently, the body weights increased significantly in both groups (p≤0.001), 3.84 kg in ALN and 3.52 kg in PBO. The results for data up to 24 months were similar, with essentially no change in weight z-scores, but increases in mean body weights of 5.4 kg in ALN and 6.80 kg in PBO (MITT-LOCF). Using the data-as-observed approach, the mean weight increases at 24 months were 6.48 kg in ALN and 9.84 kg in PBO.

Standing height:

The standing height z-scores remained approximately stable over the first 12 months in both treatment groups. Baseline height z-scores were about –3.4 in both groups.

The mean height increased significantly in both treatment groups (p≤0.001), by 3.94 (3.23, 4.64) cm in ALN and 5.92 (3.84, 8.36) cm in PBO. The growth velocities up to Month 12 were significantly different from zero in both groups [4.07 (3.22, 4.92) cm/year in ALN and 5.71 (4.13, 7.29) cm/year in PBO]. The between-group differences were not significant.

At Month 24, using MITT-LOCF, the mean increases in height were 5.55 cm (4.48, 6.63) in ALN and 7.89 cm (4.72, 11.07) in PBO. The within-group increases from baseline were significant (p≤0.001) for both groups, but the between-group difference was not (4.2.176 in NDA).

Growth velocities at Month 24 are also provided (Appendix 4.2.177). The rate of growth was 3.45 cm/year (2.77, 4.12) in ALN and 4.74 cm/year (3.50, 5.97) in PBO. The growth velocities did not differ significantly between the two treatment groups by Month 24.

Sitting height:

Sitting height z-scores were also low at baseline (-3.62 in ALN and –4.16 in PBO). Similar to standing height, there was essentially no change in sitting height z-score in either group at Month 12 (MITT-LOCF).

The sitting height increased significantly ($p \leq 0.001$) from baseline in ALN, by 2.94 cm (1.78, 4.10), and, in PBO, by 2.72 cm (0.78, 4.58, $p \leq 0.01$ for within-group comparison). Results for sitting height at 24 months are presented in 4.2.178-4.2.181 in the NDA appendix). There were no significant between-group differences in sitting height at Month 24.

Arm span:

There were significant ($p \leq 0.001$) increases from baseline in arm span in each treatment group, 6.11 cm (4.65, 8.73) in ALN and 6.22 (3.84, 9.26) in PBO. The differences between groups was not significant. At Month 24, the mean increases (MITT-LOCF) were 8.38 and 9.30 cm in ALN and PBO, respectively. The differences between the groups were not significant. The increases in arm span were even larger using data-as-observed: 11.27 and 15.09 cm in ALN and PBO respectively, at Month 24. The data-as-observed approach at Month 24 analyzed arm span from 31 ALN and 11 PBO patients, however.

Comments: Children with OI tend to grow more slowly than normals. Reproducible height determinations are difficult to obtain in patients with OI, due to bony deformities, problems with patient placement, pain, and other factors. The data submitted present no safety signal, but complete data over at least 24 months of observation will be required before a full picture of skeletal safety can emerge.

Safety histomorphometric endpoints:

Iliac crest biopsies were to be obtained in all patients at baseline and Month 24. As of the time of this submission, ten (seven ALN and three PBO) paired biopsies have been analyzed. The results are presented in 4.2.184 of the NDA. Because most of the patients have not yet been analyzed, this section cannot be reviewed except to state that at Month 24, three patients in PBO and none in ALN had an osteoid thickness of >10 mcm. Two of the seven ALN patients, but none in PBO had a mineralization lag time longer than 45 days. Thus no patient in either group had a mineralization defect at Month 24, using the pre-defined definition of an osteoid thickness of >10 mcm and a mineralization lag time >45 days.

Comments: The histomorphometry study is an essential part of the analysis of the safety of use of alendronate in this population. Final decisions regarding bone safety will have to await receipt of the complete data set. A long mineralization lag time may not be unexpected in OI patients treated with a bisphosphonate. However, osteomalacia requires the delay in mineralization plus demonstration of increased osteoid thickness. Clearly, more data are required before a judgment regarding bone safety can be made.

Healing of fractures:

As a final safety analysis, the sponsor attempted to evaluate the incidence of delayed union or frank non-union of any fractures that were observed in the baseline films. At Month 12, nine such cases were observed, 7/94 in ALN (7.4%) and 2/27 in PBO (7.4%). The denominators represent the numbers of patients with at least one evaluable set of long-bone x-rays at baseline and Month 12. Of these, delayed union was seen in three patients in ALN (3.2%) and one patient in PBO (3.7%). Non-union was seen in four patients in ALN (4.3%) and one patient in PBO (3.7%).

According to the sponsor, the healing abnormalities noted above were in existence prior to study start in at least seven of the nine patients (five in ALN and two in PBO). In the remaining two, (both in ALN), either pre-baseline films could not be obtained or the fracture occurred approximately 10 days prior to taking the baseline films.

Comments: The fracture healing findings described above are consistent with the known higher frequency of these events in children with OI, compared to normals. Unfortunately, it was not possible to do a formal comparison of the frequency of bone healing abnormalities between the two treatment groups, since not all patients had fractures at baseline and the total number of fractures present at baseline has not been evaluated. Based on the limited data available, the sponsor believes that the frequencies of bone healing abnormalities are probably similar in both treatment groups. In my opinion, it is not possible to determine, on the basis of the limited data, whether alendronate may worsen the delay in fracture remodeling that is found in patients with OI. Clearly, further data are required. Hopefully, sufficient information will be conveyed in the 24-month dataset.

IX. Summary and Conclusions

This study, which is ongoing, is the first randomized placebo-controlled trial of a bisphosphonate in pediatric patients with OI. The study enrolled 139 patients between the ages of four and eighteen years, 78 boys and 61 girls. Seventy patients were < 12 years of age and 69 were > 12. The patients were roughly equally distributed among Type III, Type IV, and Type I OI associated with chronic pain and/or > three fractures/year for the two years prior to the study, or with limb deformity requiring surgery.

The 139 patients were randomized 1:3 to receive placebo or alendronate, 5 or 10 mg/day, based on body weight stratum. Patients weighing < 40 kg at baseline (N=108) received PBO (N=24) or ALN 5 mg/day (N=84); patients ≥ 40 kg (N=31) received PBO (N=6) or ALN 10 mg/day (N=25).

The primary efficacy endpoint was change in lumbar spine (L1 to L4) BMD z-score from baseline to Month 12. Femoral neck BMD measurements were not routinely obtained, owing to poor reproducibility of this measurement in children and the lack of pediatric reference values from which to determine z-scores. As it turned out, femoral neck BMD data are available in only six patients. This is unfortunate, as the data would have given a more complete picture of the overall efficacy of alendronate. The data would have helped in understanding the discrepancy in BMD and fracture efficacy, since the radiological fractures involved long bones.

Fracture incidence was assessed as a secondary efficacy outcome. Fractures were measured as radiologically confirmed fractures (measured at baseline and at Month 12) and investigator-reported fractures (reported at any time during the study, but not necessarily radiologically confirmed). Metacarpal cortical bone width was also reported as a secondary efficacy outcome. This was measured as percent change from baseline to Month 12, to assess the effect of alendronate on cortical bone.

Exploratory efficacy outcomes included the incidence of bone pain, vertebral height, pediatric evaluation of disability, and biochemical markers of bone turnover.

Safety evaluation was performed on all patients who received study drug. The evaluation employed standard recording, reporting, and analytical methodologies for clinical and laboratory safety. In addition, special examinations included bone histomorphometry, evaluation of upper GI adverse events, and ocular adverse events.

This study was performed in strict accordance with the Written Request.

<u>Efficacy results:</u> The primary efficacy objective was clearly met, as the study demonstrated a large increase in LS BMD in association with alendronate treatment (a placebo-subtracted increase of about 1 z-score unit, corresponding to a placebo-subtracted increase of about 26%). Within-group increases from baseline (for both ALN and PBO) and between-group comparisons (ALN vs PBO) were statistically significant and sufficiently robust to withstand three separate statistical approaches. In addition to the overall increases in BMD, the responder rate in the alendronate group exceeded that in placebo.

Further analyses found no subgroup, including weight stratum, age, gender, race, pubertal status, or OI phenotype, in which the treatment effect was not manifest.

The results were essentially the same, whether measured as BMD z-score, BMD, or BMC, or whether the MITT-LOCF or data-as-observed statistical approaches were used.

Both treatment groups had (about the same) increases from baseline in LS bone area, which is indicative of skeletal growth, at both six and 12 months.

The increases in LS BMD were quite substantial, in terms of both absolute and percent changes from baseline. The increase of about 1 z-score SD unit, from –4.6 to –3.6, that was seen in the alendronate group corresponded to an absolute BMD gain of about 0.1 gm/cm^2. Since the baseline BMD was very low (about 0.375 gm/cm^2), this represented a 30% change over 12 months. It is interesting that in most studies of the effects of alendronate (or other active agents) in postmenopausal osteoporosis, the absolute mean increases in lumbar spine BMD have been approximately the same (or somewhat less, depending on the trial) over three years. However, in these trials, the baseline BMD levels have averaged around 0.7 gm/cm^2. Consequently, the percent increases have been about 5-7% within the first 1-2 years of studies in postmenopausal osteoporotic women. Since alendronate is not an anabolic agent, the results of the present study suggest that the fractional turnover rate of bone mineral is much higher in children with OI than in postmenopausal women with osteoporosis. Other factors, such as natural bone growth in a pediatric population, may have contributed to the overall effectiveness of an anti-resorptive agent. Taken together with the favorable data on areal bone growth and linear growth, these data strongly suggest that alendronate treatment is associated with an increase in mineralization in the growing bones of children with OI.

Unfortunately, the study was unable to provide useful data on BMD changes in peripheral skeletal sites, such as the hip.

Fracture outcomes: Whether measured as radiologically-confirmed or investigator-reported fractures, there was no consistent difference in this outcome between the two treatment groups. This result was somewhat surprising, in view of the very low baseline BMD in this patient population and the substantial increases in BMD and decreases in bone turnover markers associated with alendronate therapy. In addition, the results differ from the expectations that have arisen from earlier uncontrolled studies with pamidronate. It is entirely likely, however, that the increased bone fragility due to defective/deficient matrix cannot be overcome by increases in bone mineral, despite the baseline osteopenia and high turnover.

According to the sponsor, fractures could not be evaluated as an efficacy endpoint due to a multiplicity of factors. These included the polymorphic nature of many of the fractures, increase in mobility leading to a possible increase in short-term fracture risk, interim orthopedic procedures, decreasing risk with age, difficulties in consistency of limb positioning for follow-up x-rays, and less than ideal rater reliability among radiologists. In addition, the sponsor claims that the small size of the population and the relatively low fracture rate ("only" 54% of patients experienced at least one new fracture in the first 12 months) limited the power to detect treatment

differences. There were 104 new radiologically confirmed fractures in 94 alendronate patients and 30 in 27 treated with placebo, yielding essentially the same fracture rate in both groups (1.1 fracture/patient/year). Given this number of fractures, it is surprising to me that no consistent trend was observed, if alendronate was indeed effective. Similar results were obtained in the analysis of investigator-reported fractures. Here, the incidence of fractures was slightly less in ALN, compared to PBO. In addition, the cumulative percent of patients with at least one investigator-reported fracture up to Month 12 was numerically lower in ALN at each three-month interval, compared to PBO. However, there was no significant difference in time to first fracture although the time was numerically longer in ALN, compared to PBO. It will be important to evaluate the 24-month data to determine if this trend increases.

There was an increase in cortical width of the second left metacarpal bone of 10.3% in ALN and 3.1% in PBO. The between-group differences were not significant. However, the results are encouraging, in view of the fact that lumbar spine is very high in cancellous bone.

There was no statistically significant difference in percent of patients with bone pain, frequency of bone pain, or percent of patients reporting waking at night with bone pain at Month 12, although there was a decline in these parameters in both groups.

Biochemical analyses strongly supported the pharmacodynamic effects of alendronate in suppressing markers of bone turnover.

Other exploratory analyses, such as the pediatric evaluation of disability, also failed to detect a treatment-group difference at 12 months.

Thus, 12 months of treatment with alendronate dramatically improved lumbar spine BMD, relative to placebo, and demonstrated the expected pharmacodynamic actions on mineral metabolism in pediatric patients with OI. However, there were no discernible clinical benefits. A trend in favor of alendronate was seen in the cumulative proportions of patients with investigator-reported fractures. This trend was not seen in other fracture analyses. One must await the 24-month fracture data to determine the clinical efficacy of alendronate in treating this patient population.

Safety:

This study randomized 109 patients to ALN and 30 to PBO. Of these, 89 (81.7%) of ALN and 29 (96.7%) of PBO took at least 12 months of study medication (within pre-defined relative day range). The mean total duration of exposure in ALN was 317.7 days (range, 40 to 444 days) and, in PBO, 348.5 days (range, 270 to 378 days). The median exposure time was the same in both groups (356 days).

The study is ongoing, and, at the time of the submission 49 patients had received alendronate for up to two years. The sponsor included safety data past 12 months, and all safety data were analyzed in this review. For all safety data past 12 months (i.e., "Results up to 24 Months"), the median exposure times were 545 days in ALN (range 40-751) and 612 days in PBO (range 295-732).

Based on data submitted, the overall safety and tolerability of alendronate in the pediatric population with OI were favorable. The adverse event profile of alendronate was comparable with that of placebo, both in data up to 12 and up to 24 months. Six patients in the entire study population experienced at least one serious AE (excluding fractures) during the 12-month double-blind treatment period: Four in ALN (3.7%) and two in PBO (6.7%). Four more patients in ALN had a serious clinical adverse event after Month 12. I have reviewed the clinical reports and have concluded that it is possible that vomiting in two patients was associated with alendronate. In addition, one case of leukopenia was reported in a patient taking alendronate. This is not known to occur in adults, but should be followed as a safety signal in children whether or not the drug is approved for this indication. Patients treated with alendronate had growth velocities (standing and sitting) that were at least as high as those of patients treated with placebo for the first twelve months; data available up to 24 months also showed no treatment-group differences in height velocities. A separate upper GI safety analysis was performed, and there was no indication that alendronate is associated with an increase in GI toxicity in this population, on the basis of the submitted data. However, I have raised the possibility that alendronate contributed to the vomiting that was associated with dehydration in two patients.

There were no deaths during the study (either in the first 12-month period or in the data reported for the 24-month period).

X. RECOMMENDATIONS

(b) (4)

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XI. Appendix

Financial disclosure data

Merck has submitted the required financial disclosure information for investigators and sub-investigators in the study. There were 51 investigators and sub-investigators. Forty-nine returned financial disclosure forms and were certified as having no financial arrangements as defined in 21 CFR 54.2. Two investigators/sub-investigators did not provide the requested information, despite multiple attempts by Merck to obtain the documentation. These investigators/sub-investigators were at two different study sites. The names of all 49 investigators/sub-investigators who provided information and the two who did not provide information are presented in the NDA.

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/s/

Bruce Schneider
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