DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-560

Merck Research Laboratories
Attention: Michele Flicker, MD, PhD
Director, Regulatory Affairs
P.O. Box 2000
Rahway, NJ 07065

WRITTEN REQUEST
Amendment #1

Dear Dr. Flicker:

Reference is made to your correspondence dated April 23, June 21, July 2, August 6, and October 25, 2001, requesting changes to FDA's October 27, 2000, Written Request for pediatric studies for alendronate sodium.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on October 27, 2000, remain the same.

Study 1, clinical study

- *Type of study:* A randomized, double-blind, placebo-controlled, multicenter study.

- *Study Design:* A multicenter, randomized, double-blind, placebo-controlled, parallel group study of pediatric patients with osteogenesis imperfecta. During the double-blind period, patients should receive once-daily placebo or alendronate 5-or 10-mg tablet, depending on body weight. All patients will receive alendronate in an open-label extension immediately following the first positive efficacy analysis (either following the interim analysis, or in the event the interim analysis does not fulfill the efficacy criteria, following the final analysis of 12-month bone mineral density [BMD] values for all children in the study). Open-label extension data beyond the 12-month time point are not required to fulfill the Written Request. In the event that efficacy has not yet been demonstrated (i.e., non-statistically significant results), but the Data Safety Monitoring Board (DSMB) believes there are sufficient efficacy and safety to consider early transition to alendronate for those patients for whom 12-month BMD data have been obtained, you should consider that position and, as appropriate, discuss with the Agency a further amendment to the Written Request. Patients who received 5-mg once-daily alendronate during the double-blind period may be switched

to 35-mg once-weekly alendronate, patients who received 10-mg once-daily alendronate during the double-blind period may be switched to 70-mg once-weekly alendronate, and patients who were on placebo and weighed less than 40 kg at baseline may receive 35 mg once-weekly, and patients who were on placebo and weighed greater than or equal to 40 kg at baseline may receive 70 mg once-weekly. All patients should receive supplemental calcium and vitamin D as appropriate standard care.

- *Age group of patients to be studies:* Four to eighteen years of age.

- *Number of patients to be studied:* A total of approximately 120 patients or more should be enrolled into the study. Of these, approximately 80 patients or more should be randomized to receive alendronate, and approximately 30 to 40 patients should be randomized to receive placebo.

- *Entry criteria:*

  - pediatric patients with phenotypic osteogenesis imperfecta type III or IV.
  - pediatric patients with phenotypic osteogenesis imperfecta type I with chronic pain and/or > 3 fractures (including vertebrae) per year due to minimal trauma during the previous 2 years, or with limb deformity requiring surgery.
  - patients should be capable of standing or sitting upright for at least 30 minutes following dosing and complying with all dosing instructions.
  - patients regularly using drugs that alter gastric pH (i.e., H2 blockers, antacids) and patients who are pregnant should be excluded from participation in the study. However, calcium supplements will be allowed if used to achieve an adequate daily calcium intake.

- *Clinical endpoints:* The primary efficacy endpoint should be the change in lumbar spine bone mineral density from baseline to month 12. Month 12 is defined as study day 365 (as measured from the first day of treatment with double-blind medication) plus or minus 90 days. Fracture rate should be a secondary endpoint. Additional endpoints should include bone pain, height, and biochemical markers of bone turnover.

- *Study evaluations:* Study evaluations should include measurement of serum levels of calcium, phosphate, PTH, and vitamin D, and urine levels of calcium (corrected for creatinine). Assessment of bone histomorphometry following bone biopsy should also be conducted. Bone biopsies will be performed at baseline and prior to transition of each patient from the double-blind phase of the study to the open-label extension. Histomorphometric analyses of these biopsies will be reported as noted below in the ***Statistical information*** and ***Timeframe for submitting reports of the studies*** sections.

- *Drug information:*

Dosage Form:	Tablets
Route of administration	Oral
Regimen- Double blind period:	Patients < 40 kg 5 mg once daily or placebo
	Patients ≥ 40 kg 10 mg once daily or placebo
Regimen- Open label period:	Patients < 40 kg 35 mg once weekly
	Patients ≥ 40 kg 70 mg once weekly
Formulation:	Same as marketed

- *Statistical information:* Change from baseline in lumbar spine BMD Z-score at one year will be compared between alendronate and placebo using ANCOVA adjusted for baseline. The primary analysis population will be the intent-to-treat (ITT) population consisting of all randomized patients with an observation at baseline and at least one on-treatment observation.

  An interim analysis will examine the primary endpoint using all data available as of March 31, 2001. The primary analysis population will be the intent-to-treat (ITT) population consisting of all patients who have been randomized by March 15, 2000, and who have an observation at baseline and at least one on-treatment observation. Patients with data at 6 months only will have their 6-month values included in the analysis. The analysis will be conducted using a nominal 1% Type I error rate. Efficacy will have been demonstrated, and consideration given in conjunction with the recommendation of the DSMB to terminate the double-blind portion of the study, if the p-value of the interim analysis is smaller than 1%. All patients should then receive open-label, once-weekly alendronate for a total of up to three years of treatment. If the interim analysis fails to document efficacy, all patients should continue in their respective treatment groups at least until the final analysis of the blinded portion of the trial (i.e., the analysis of 12-month BMD data for all children in the study). The term "12 month BMD" is defined as the BMD determined on study day 365 (as measured from the first day of treatment with double-blind medication) plus or minus 90 days. In the event that efficacy has not yet been demonstrated, but the Data Safety Monitoring Board (DSMB) believes there to be sufficient efficacy and safety to consider early transition to alendronate for those patients for whom 12-month BMD data have been obtained, you are encouraged to consider that position and, as appropriate, to discuss with the Agency a further amendment to the Written Request.

  The final analysis, if required, will be conducted at a nominal significance level determined in order to maintain an overall 5% Type I error rate for the entire study. If efficacy is demonstrated in the final analysis, all patients should then receive open-label, once-weekly alendronate for a total of up to three years of treatment. If efficacy is not demonstrated by the final analysis, the trial should be terminated unless the DSMB believes that sufficient efficacy and safety have been demonstrated to warrant consideration of alternatives to study termination. At that time, although the Written Request will be fulfilled with regard to Study

1, you are encouraged to consider that position and, as appropriate, to discuss with the Agency a further amendment to the Written Request.

An interim analysis approach that includes all of the data in the decision-making process while maintaining the primacy of the 12-month BMD measurement will be used by the DSMB to determine whether or not to recommend stopping the double-blind phase of the trial. Details will be described in the Data Analysis Plan.

Submission of placebo-controlled data following the interim analysis (if efficacy is demonstrated), or the final analysis (i.e., the analysis of 12-month BMD data for all children in the study) will constitute completion of the study and fulfillment of the Written Request with regard to study 1. The subset of the bone histomorphometry results available by March 1, 2002, should be submitted with the final analysis**.** While not required to fulfill the Written Request, a follow-up report including the data from the double-blind study and its open-label extension, and the remainder of the bone histomorphometry data, should be submitted when available.

Study 2, clinical pharmacology study

- *Number of patients to be studied:* A minimum of 16 patients will be studied.

- *Entry criteria:*

  - pediatric patients with phenotypic osteogenesis imperfecta type I, III, or IV.
  - patients should be capable of standing or sitting upright for at least 2 hours following dosing and complying with all dosing instructions.
  - patients using drugs that alter gastric pH (i.e., H2 blockers, antacids) and patients who are pregnant should be excluded from participation in the study.

- *Statistical information:* A sample size of 8 patients in each body weight category (< 40 kg and ≥ 40 kg) should permit the estimation of the oral bioavailability of the 35-mg tablet (< 40 kg) and 70-mg tablet (≥ 40 kg) as compared to the 125-µg IV to be within 77% for each body weight category, but the actual precision to be observed will depend upon the variability in the patient population.

Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before July 31, 2003. If the interim analysis is positive (i.e., if efficacy is demonstrated), submit both the interim clinical study results and the clinical pharmacology study results for at least 16 patients to the Agency on or before June 30, 2002. Should the interim analysis not be positive, submit clinical study results for the final analysis of 12-month BMD data for all children in the study, the subset of the bone histomorphometry results available by March 1, 2002, and the clinical pharmacology study results for at least 16 patients by July 31, 2003**.** The follow-up report including all data from the double-blind portion of the trial and its open-label extension should be submitted to the Agency by

December 31, 2004. Also, the remainder of the bone histomorphometry results will be submitted with this follow-up report.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Randy Hedin, Senior Regulatory Management Officer, at 301-827-6392.

Sincerely yours,

{See appended electronic signature page}

Sandra Kweder, M.D.
Acting Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sandra L. Kweder

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