CD has been checked for computer viruses using Norton AntiVirus for Windows NT Workstation (with virus definitions dated 09/10/99), and is hereby certified to be virus-free.

Should you have any further questions regarding this submission please contact Mr. Shawn McLaughlin of my staff at (650) 225-1915.

Sincerely,

Roxanne Bates for RLG

Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs

19676-103 sub rer

Genentech, Inc.

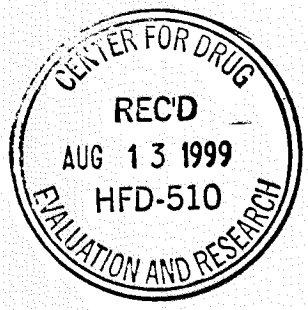
1 DNA Way
South San Francisco, CA 94080-4990
(650) 225-1000
FAX (650) 225-6000

DUPLICATE

SUPPL NEW CORRESP
SE8-013-INC

August 11, 1999

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room, 14B-03
5600 Fishers Lane
Rockville, MD 20857



Subject: **NDA 19-676, S-013**
Nutropin® [somatropin (rDNA origin) for injection]
Supplement - Additional Label Claim
Bone Mineral Density
Request for Waiver of Requirement to Conduct Pediatric Studies
[21CFR 201.23(a)]

Dear Dr. Sobel:

Reference is made to our Supplemental New Drug Application, NDA 19-676, S-013, for Nutropin® [somatropin (rDNA origin) for injection], submitted on January 29, 1999 providing clinical data to support an additional label claim of improved bone mineral density (BMD) with Nutropin treatment in adults with growth hormone deficiency.

Further to a telephone conversation with Crystal King of your office, and in regard to the FDA Final Rule: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, we are requesting a waiver from the requirements of 21CFR 201.23(a), under subpart (c)(1), on the basis that adequate pediatric studies have already been performed with Nutropin.

The studies already performed in pediatrics include:

- Studies 86-061 and 87-070 in NDA 19-676, for pediatric growth hormone deficiency.
- Studies 87-069, M0079g, and M0221g in NDA 20-168, for growth failure associated with chronic renal insufficiency.
- Study 85-044 in NDA 20-656, for short stature associated with Turner syndrome.
- Study M0380g in IND [redacted] for pubertal dosing in pediatric growth hormone deficiency.
- Phase IV study P0583n, and on-going National Cooperative Growth Study.

Should you have any further questions regarding this submission please contact Mr. Shawn McLaughlin of my staff at (650) 225-1915.

Sincerely,

Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs

19676-098 sub ss

Genentech, Inc.

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South San Francisco, CA 94080-4990
(650) 225-1000
FAX: (650) 225-6000

August 10, 1999

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room, 14B-03
5600 Fishers Lane
Rockville, 20857

Attention: Ms. Joy Mele
Dr. Saul Malozowski

Subject: **NDA 19-676, S-013**
Nutropin® [somatropin (rDNA origin) for injection] Adult Growth Hormone Deficiency
Supplement - Additional Label Claim
Bone Mineral Density
Response to Request for Information

Dear Dr. Sobel:

Reference is made to our Supplemental New Drug Application, NDA 19-676, S-013, for Nutropin® [somatropin (rDNA origin) for injection], submitted on January 29, 1999, providing clinical data to support an additional label claim of improved bone mineral density (BMD) with Nutropin treatment in adults with growth hormone deficiency.

In response to Ms. Joy Mele's July 30, 1999 request for additional information for her review, and further to a telephone discussion between Ms. Mele and Genentech biostatistician Joyce Baptista, enclosed are additional BMD data from study M0431g, as well as a copy of the Final Report for M0431g which was previously submitted in NDA 19-676, S-009, on December 13, 1996.

19676-097 sub ss

An archival copy of the data only is provided on CD-ROM, and paper copies of both data and the M0431g report have been submitted for Ms. Mele and Dr. Malozowski. The CD has been checked for computer viruses using Norton [redacted] and is hereby certified to be virus-free.

Additionally, in response to Dr. Saul Malozowski's questions regarding the use of DEXA scanners in study M0381g, Genentech went to great lengths to assure quality control throughout the study. Sites were instructed to use the same machine for serial DEXA measurements of each patient. Genentech also employed the [redacted] division to develop a DEXA quality control and procedures manual, which was included in the study guide provided to the sites. [redacted] also performed cross-calibration of equipment (using phantoms shipped to all sites), data management (scan review and outlier analysis), and database review. This included data from both Hologic and Lunar scanners. [redacted] provided Genentech with an electronic database following their extensive validation, which was compared and found to be in close agreement to the data submitted to Genentech and incorporated into the SAS database ($r > 0.99$).

We hope this information is helpful. Should you have any further questions regarding this submission please contact Mr. Shawn McLaughlin of my staff at (650) 225-1915.

Sincerely,

Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs

19676-097 sub ss

Genentech, Inc.

NDA SUPPLEMENT
SE8-013 - BM

ORIGINAL

1 DNA Way
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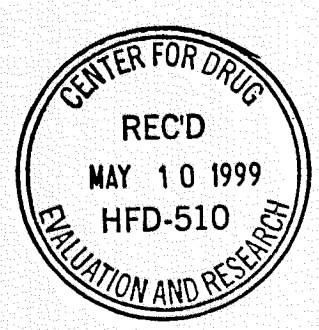


May 7, 1999

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room, 14B-03
5600 Fishers Lane
Rockville, MD 20857

Attention: Dr. Saul Malozowski

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Subject: **NDA 19-676**, S-013
Nutropin® [somatropin (rDNA origin) for injection]
Adult Growth Hormone Deficiency
Supplement - Additional Label Claim
Bone Mineral Density
Response to Request for Information

Dear Dr. Sobel:

Reference is made to our Supplemental New Drug Application, NDA 19-676, S-013, for Nutropin® [somatropin (rDNA origin) for injection], submitted January 29, 1999, providing clinical data to support an additional label claim of improved bone mineral density (BMD) with Nutropin treatment in adults with growth hormone deficiency.

In response to Dr. Saul Malozowski's April 23, 1999 request for additional information regarding statistical analyses, we submit the following:

The objective for study M0381g, Phase II/III Study of Safety and Efficacy of Nutropin in Previously Treated Growth Hormone-Deficient Adults, was to determine the effects of prolonged treatment with Nutropin in young adults with

childhood-onset GH deficiency. They were all previously treated with GH and then off therapy for a period before restarting GH (at one of two doses) or placebo in the study. The original primary endpoints for the study were the change in percent lean body mass and physical performance. Prior to unblinding the randomization, the primary endpoint was modified to include total body percent fat, trunk percent fat, and total body percent lean, as assessed by DEXA scan. One of the protocol-specified secondary objectives was to determine the impact of therapy on bone mineral density, also assessed by DEXA scan.

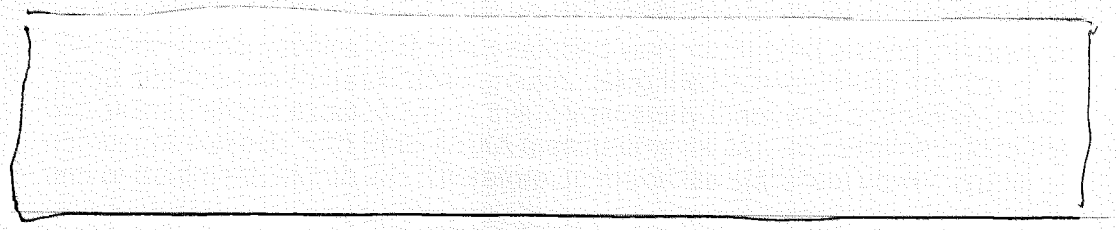
The statistical analysis section of the M0381g **protocol** (Section 3.6) states:

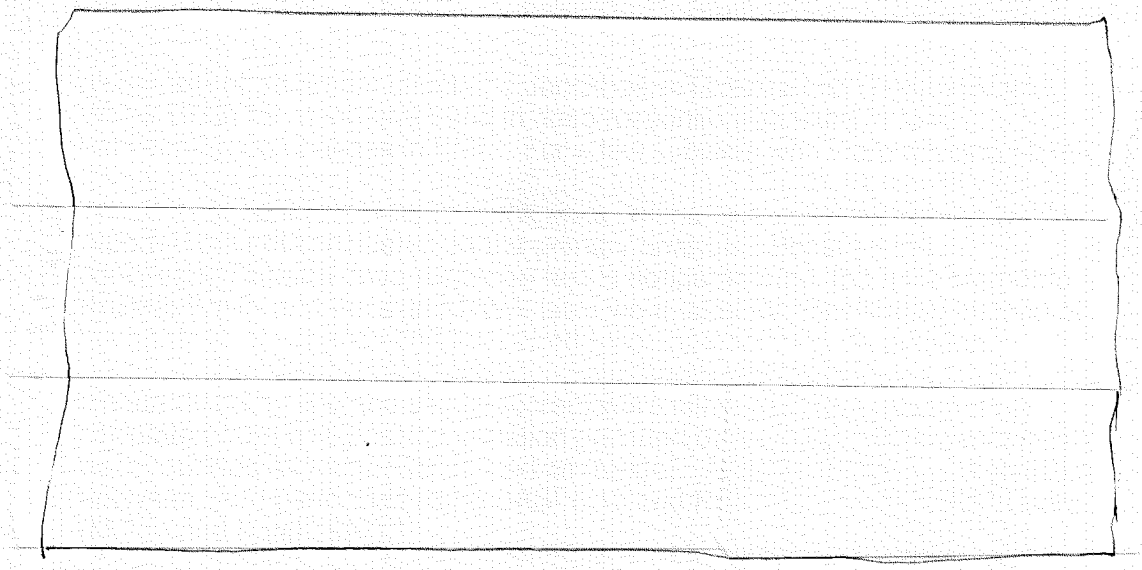
> "The placebo and the two growth hormone groups will be compared with each other using two-tailed t-tests, each at an alpha level of 0.05/3=0.0167, the smaller alpha level being used to adjust for multiple comparisons. These t-tests were to be performed using change from baseline for both primary endpoints...Comparison between baseline, 12- and 24-month results will also be made within each group using the paired t-test. For body composition results, data from the post-treatment visits 4-6 weeks after the Month 24 visit will be used in the primary analysis. Between-group comparisons of 12- and 24-month results for all endpoints will also be made using analysis of covariance with the corresponding baseline results as covariates. The same analyses will be made for other endpoints including results of psychological tests, bone density measurements, cardiac parameters, lipid profile and immune tests."

Please note that a copy of the M0381g protocol was submitted to NDA 19-676, S-013, on March 19, 1999, in response to a request from the reviewers.

Comment: As you are probably aware, the post-treatment DEXA measurements were to be used for body composition calculations due to the effect of GH on water balance and, in turn, the effect of this on lean mass calculations. Since this does not affect bone mineral measurements, and because more data were available at the end of the study (Month 24) than at post-treatment, the Month 24 data were used in the bone density analyses.

The BMD **Label Claim submission** of 29 January, 1999, specified the following statistical methods (Section 2):





Comment: As stated in the BMD submission statistical methods above, to maximize statistical power in one global test of treatment effect, the Jonckheere-Terpstra test for monotone trend in dose response was used to test between-group changes in BMD. By this test, a significant dose response was observed for the percent change in Spine BMD from baseline to Month 24 ($p = 0.018$). The within group changes were highly significant in both the low and high GH dose groups by the signed rank test ($p = 0.0067$ and 0.0009, respectively).

The percent change in BMD (gm/cm^2) is the standard parameter used to assess treatment interventions for osteoporosis (see enclosed references: Liberman 1995, Delmas 1997, McClung 1998) and has been used as the primary endpoint in prevention studies for FDA-approved drugs. It is noteworthy that the BMD changes observed with GH in this population are of the magnitude seen with these first-line therapies for osteoporosis/osteopenia.

Baseline z-scores were provided to illustrate the effect of GH deficiency on BMD compared with age- and sex-matched controls. Changes in z-scores were also provided to help illustrate the clinical significance of the treatment effect with respect to subsequent fracture risk, as discussed in the submission.

As was mentioned in our teleconference on April 27, we feel that the addition of a figure to the PI could be very helpful to prescribers with respect to the time course and pattern of change. In particular, Figure 7 of the submission would nicely complement the text that we have already proposed in the submission. We will submit a revised package insert reflecting this change soon.

We hope this information is helpful. Should you have any further questions regarding this submission please contact Mr. Shawn McLaughlin of my staff at (650) 225-1915.

Sincerely,

Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs

Fax cc: Dr. Saul Malozowski

Genentech, Inc.

1 DNA Way
South San Francisco, CA 94080-4990
(650) 225-1000
FAX: (650) 225-6000

March 9, 1999

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room, 14B-03
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 19-676**, S-013
Nutropin® [somatropin (rDNA origin) for injection]
Supplement - Additional Label Claim
Bone Mineral Density
Request for Information: New CD-ROM

Dear Dr. Sobel:

Reference is made to our Supplemental New Drug Application, NDA 19-676, S-013, for Nutropin® [somatropin (rDNA origin) for injection], submitted January 29, 1999, providing clinical data to support an additional label claim for improved bone mineral density (BMD) with Nutropin treatment in adults with growth hormone deficiency.

In response to Dr. Malozowski's notification that the previous CD-ROM sent on March 4, 1999 did not contain the correct files due to an inadvertent error, we are sending new copies of these disks.

This submission contains a new CD-ROM containing the additional data for patients, including demographics and concomitant medications, requested by Dr. Malozowski on March 1, 1999. This CD is designated as Version 2, 9 March 1999 to distinguish it from the faulty CD sent on 4 March 1999.

19676-086 sub ss

We apologize for the inconvenience. Should you have any further questions regarding this submission please contact Mr. Shawn McLaughlin of my staff at (650) 225-1915. For technical assistance please call Mr. Scott Moore at (650) 225-7137.

Sincerely,

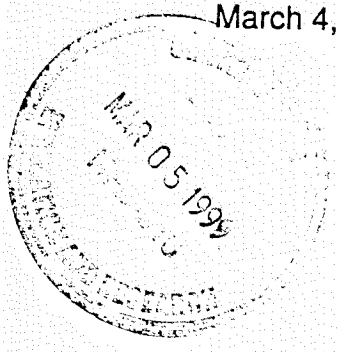
Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs

cc: Dr. Saul Malozowski

Genentech, Inc.

1 DNA Way
South San Francisco, CA 94080-4990
(650) 225-1000
FAX: (650) 225-6000

March 4, 1999



Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room, 14B-03
5600 Fishers Lane
Rockville, MD 20857

Attn: Saul Malozowski, M.D.

Subject: **NDA 19-676**, S-013
Nutropin® [somatropin (rDNA origin) for injection]
Supplement - Additional Label Claim
Bone Mineral Density
Request for Information

Dear Dr. Sobel:

Reference is made to our Supplemental New Drug Application, NDA 19-676, S-013, for Nutropin® [somatropin (rDNA origin) for injection], submitted January 29, 1999, providing clinical data to support an additional label claim for improved bone mineral density (BMD) with Nutropin treatment in adults with growth hormone deficiency.

This submission contains additional data for patients, including demographics and concomitant medications, as requested by Dr. Saul Malozowski on March 1, 1999. These tables are attached in hard copy as well as on the enclosed CD-ROM.

19676-085 sub ss

Also, per Dr. Malozowski's request, we have enclosed one additional desk copy of the CD-ROMs for this supplement in a separate folder.

Should you have any questions regarding this submission please contact Ms. Fiona Cameron of my staff at (650) 225-1818.

Sincerely,

Joyce L Chaienza for

Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs

Genentech, Inc.

1 DNA Way
South San Francisco, CA 94080-4990
650 225 1000
FAX (650) 225-6000

November 5, 1999

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room, 14B-03
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 19-676, S-013**
Nutropin® [somatropin (rDNA origin) for injection]
Adult Growth Hormone Deficiency
Supplement—Additional Label Claim
Bone Mineral Density
Information Amendment

Dear Dr. Sobel:

Reference is made to our Supplemental New Drug Application, NDA 19-676, S-013 for Nutropin® [somatropin (rDNA origin) for injection], providing clinical data to support an additional label claim of improved bone mineral density (BMD) in adults with growth hormone deficiency. The original supplement was submitted on January 29,1999 and final draft labeling was submitted October 29, 1999.

This submission provides revised final draft labeling to correct two minor typographical errors that were noted by the Agency in our October 29 submission and communicated by Ms. Crystal King.

- (Page 14 of label, 2nd paragraph, 3rd sentence) [redacted] has been corrected to be [redacted]

- (Page 16, CONTRAINDICATIONS, 1st paragraph): [redacted] has been corrected to be [redacted] (Please note that this error appeared in the draft labeling submitted to this supplement, but the wording is correct in our current FPL for Nutropin)

In addition, this submission provides the following items requested by Ms. King on November 1, 1999 that were not included in the original supplement:

- Patent information
- Patent certification
- Debarment certification
- Categorical exclusion statement for Environmental Assessment

The enclosed CD-ROM contains an annotated and clean version of the final draft Nutropin PI, as well as the above items. This CD has been checked for computer viruses using Norton AntiVirus for Windows NT Workstation (with virus definitions dated 09/10/99), and is hereby certified to be virus-free.

Should you have any further questions regarding this submission please contact Mr. Shawn McLaughlin of my staff at (650) 225-1915.

Sincerely,

Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs

HFD-510 DMEDP

Memo

To: The File

From: Crystal King, Regulatory Project Manager

Date: 11/06/99

Re: Bone Mineral Density Supplement Labeling

We have agreed upon and accepted the draft labeling as submitted by Genentech on November 5, 1999.

/S/ 11/8/99
Joy Mele, M.S.
Biometrics Reviewer

/S/ 11/5/99
Saul Malozowski, M.D., Ph.D.
Medical Reviewer and Team Leader (Acting)

cc: NDA 19-~~656~~676/S-013
NDA 20-522/S-009
Division Files
HFD-510: S.Malozowski/J.Mele/C.King

Date: November 1, 1999 /S/

From: Saul Malozowski
Medical Officer

Subject: NDA 19-676 SE1-013, Nutropin changes in bone mineral density; Team Leader Memo

To: The file

I concur with the contents of this NDA review and with the recommendations proposed by the reviewers.

concur /S/
11-30-99

APPEARS THIS WAY
ON ORIGINAL