3. Demonstration of Product Comparability
   Question: Does the agency concur with the plan?
   Answer: Yes, from CMC point of view
   CofAs need to be included

4. Microsphere Sterility Testing
   Question: Does the agency agree with the plan presented for routine evaluation of microsphere sterility?
   Answer: Yes
   Validation of the [redacted] method is required

5. Isolator Qualification and Routine Monitoring
   Question: Are there any concerns with this approach?

   Answer: Dr. Cooney and Dr. Hussong noted that they are "comfortable" with this plan. It was also noted that [redacted] should "stay in contact" with the agency and should submit a final validation package to include a protocol, summary of acceptance criteria, and data.

6. [redacted] Simulation
   Question: Are process simulation studies still needed?
   Answer: Yes, at this time they are needed. It was also noted that routine reevaluation was still necessary also.

   Question: Is the proposal acceptable?
   Answer: Yes, Dr. Cooney and Dr. Hussong requested that [redacted] keep in touch with the agency during the pre-NDA process. The weak point in the process was identified as the vial-filling step.

[redacted] /S/ 2-12-98

Signature, Minutes Preparer: Michael F. Johnston, Project Manager

Concurrence: Dr. Stephen Moore (Meeting Chair): [redacted] /S/ 2/11/98

Clearances: Wberlin/SMoore/PCooney/DHussong

cc: IND File: IND [redacted]
HFD-510: SMoore/WBerlin/MJohnston
HFD-160: PCooney/DHussong

w Attachment

ORIGINAL

IND [redacted]

5.1

MEETING MINUTES

Meeting Date: October 28, 1997 10:30 AM (Meeting Concluded at 11:45 AM)

Drug: ProLease hGH

Indication: GH Deficiency Sponsor: [redacted]

Meeting Type: Pre-Phase III

Attendance: M. Johnston, CSO (recorder)
S. Sobel M.D. Division Director
J. Mele, M.S.. (Biometrics)
A.Fleming M.D. (Chair)
S. Malozowski, M.D. (Medical Officer)
H. Ahn, Ph.D. (Biopharm Tm. Ldr)

Attendance (Sponsor): See Attachment #1

Meeting Objectives:
1. Review of Phase II Protocols
2. Review of Phase III Protocols
3. Discussion on Questions

I. INTRODUCTIONS: Mr. [redacted] started by thanking FDA for the meeting and introductions went "around the table." He then reviewed the meeting agenda.

II. CLINICAL UPDATE (Dr. Wortel): As per the premeeting package (with supplement), Dr. [redacted] reviewed the results to date of the phase I/II study (# [redacted]03-002). Questions were raised concerning patient injection site pain. Dr. Malozowski noted that 40% of the patients required at least 2 injections and encouraged the sponsor to determine which injection site was producing the least pain. Dr. Ahn asked if PK studies had been done at various injection sites. The sponsor noted that in using the abdomen, thigh, and arm, they have seen no variability. The sponsor noted that they have no PK studies planned at this time.

The sponsor noted that they plan to exclude hypoglycemia and seizure patients in the phase III study. Dr. Sobel noted that the proposed phase III study was not a controlled study but relied on historical control. Dr. Attie agreed.

Dr. Fleming noted that the product appears to offer reduced efficacy and demonstrating efficacy (greater than or equal to 8 cm/year) should be the goal of the study. Dr. Malozowski noted that the expectation (see page 39, paragraph 3 of premeeting package) of 9 cm/year was very optimistic. Dr. Mele discussed that the sponsor should establish what is NOT an acceptable growth rate (i.e. lower acceptable limit).

Dr. Fleming noted that longer duration (40-50 patients with one year of data) was desirable. It was noted that labelling could include the results of 60 patients (30 drug/30 placebo). Dr.

[redacted]

[redacted]

January 29, 1998

Mr. Michael Johnston
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Endocrine Drug Products, HFD-510
Parklawn Building, Room 14B04
5600 Fishers Lane
Rockville, MD 20857

RE: IND # [redacted]
[redacted] hGH
Serial #029
General Correspondence

VIA FACSIMILE: (301) 443-9282

Dear Mike:

As requested, below please find a list of [redacted] and Genentech attendees for the pre-NDA CMC meeting held yesterday. I am also including as an attachment to this letter a typed version of the meeting minutes. Under the release testing topic, I have added information in brackets to clarify a comment.

[redacted]

	Vice President, Regulatory Affairs and Quality Assurance
	Vice President, Operations
	Senior Scientist
	Director, Process Development Engineering
	Director, Manufacturing Technology
	Associate Director, Quality Control
	Associate Director, Regulatory Affairs

Genentech:

Robert Baird	Director, Quality Assurance Validation
Jack Regan	Director, Pharmaceutical Manufacturing
Michael Wiebe	Director, Quality Control/Quality Assurance
Art Blum	Director, Regulatory Affairs
Peter Rauenbuehler	Assistant Director, QC Marketed Products

If you require any additional information, please do not hesitate to contact me at (617) 494-0171.

Sincerely,

[redacted]

ATTACHMENT (1)

Fleming also asked what the sponsor had seen concerning antigenicity. Dr. Wortel noted that patients (who were negative at baseline) did not develop antibodies. Some naive patients did develop low antibody titers (< 1.9) after 3-6 months.

III. QUESTIONS /CONCLUSION: Mr. [redacted] addressed the questions and meeting results as follows:

1. The sponsor noted that they would remove the 9 cm value for growth and look at a target/confidence interval approach. The efficacy results would include both the phase I and phase II data. It was emphasized to the sponsor that they use valid testing methods in assessing GH deficiency.

2. Orphan Status: Mr. [redacted] asked whether the product could be considered for orphan status as a "major improvement to patient care." Both Dr. Sobel and Dr. Fleming felt that this was reasonable.

3. [redacted] asked about approval for other GH indications (CRI, Turners, Adult GH Deficiency). Dr. Sobel and Fleming disagreed with the sponsor's opinion that only PK data would suffice for this. Dr. Sobel noted that different patient dynamics are present and that patients may not reach the final height achieved with daily dosing.

Signature, Minutes Preparer: /S/ Michael F. Johnston, Project Manager

Concurrence: Dr. Fleming(Mtg Chair): /S/ 11/14/97

Concurrence Dr. Sobel: /S/ 11-14-97

Clearances: SMalozowski11.2.97/GFleming11.3.97/Ahn11.12.97/Mele11.13.97

cc: IND File: IND [redacted]
HFD-510: GFleming/SMalozowski/MJohnston/SSobel/
HFD-870: [redacted]/HAhn
HFD-715: JMele/ENevius

[redacted]

APPEARS THIS WAY
ON ORIGINAL

Genentech, Inc.

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

December 14, 1999

Solomon Sobel, M.D.
Director
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: NDA 21-075 Nutropin Depot™
Amendment to a Pending Application
Item 2—Labeling
Item 4—Chemistry, Manufacturing, and Controls

Dear Dr. Sobel:

Genentech, Inc. is submitting the enclosed information to NDA 21-075 for Nutropin Depot [somatropin (rDNA origin) for injectable suspension]. This information consists of a revised [redacted] specification for [redacted] Bulk rhGH Microspheres, and a Phase IV commitment related to this assay, as discussed with Dr. Robert Shore and Dr. Hae-Young Ahn of Biopharmaceutics. A further minor revision to the package insert and a clean version of the revised package insert are also provided. A desk copy of this document is provided in a black binder for Ms. Crystal King, P.D., M.G.A., Project Manager. The CMC review copy is provided in a red binder and an additional copy has been provided in an orange binder for Dr. Shore. Field copies of this Chemistry information have also been submitted to the San Francisco and Boston District offices.

An electronic archival copy of this submission on one CD has been submitted under separate cover to the CDER Central Document Room, according to the Guidance for Industry—Providing Regulatory Submissions in Electronic Format—General Considerations. Text is provided in Adobe Acrobat pdf format.

For help or information concerning any technical issues associated with the CD or electronic documents, please contact Mr. Scott Moore at (650) 225-7137 or Mr. Jan Van Gelder at (650) 225-1558. Please contact Ms. Fiona Cameron, Senior Manager, at (650) 225-1818, by fax at (650) 225-1397 or by email at cameron.fiona@gene.com if you have any other questions regarding the content of the application. We look forward to working with you during your review of this information.

Sincerely,

Joyce L Chavez for

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

APPEARS THIS WAY
ON ORIGINAL

Printed by Crystal King

Electronic Mail Message

Date: 14-Dec-1999 09:47am
From: Fiona Cameron
cameron2@gene.com
Dept:
Tel No:

TO: kingc (kingc@A1)
TO: shorer (shorer@A1)

Subject: Nutropin Depot - Assay Spec, Commitment and Final PI

Nutropin Depot NDA 21-075

Dear Crystal and Rob:

Attached are the following per our conversations today:

1. Revised document from the CMC section on specifications, showing the new specifications as agreed with Drs Ahn and Shore today, as well as the agreed-on commitment to work on a new [redacted] and revise the specification within one year. (4a3f2rev.doc)

2. Marked up revised PI showing the one change (addition of "mean") (From GNE121399.doc)

3. Clean Final PI (Final2PI121399.doc)

I'll also fax Crystal a copy of the cover letter which will accompany formal submission of these documents. We will send the information in by courier tomorrow, so you should receive it on Wednesday.

Please let me know if I can provide any further assistance.
Kind regards
Fiona

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ON ORIGINAL

BEST POSSIBLE COPY

4.A.3.f.2 [redacted] rhGH Bulk Microspheres

SPECIFICATIONS AND CERTIFICATES OF ANALYSIS

Refer to:

Table 1 [redacted] rhGH Bulk Microspheres—Tests and Specifications.

This section contains a summary of the specifications and methods employed for [redacted] rhGH Bulk Microspheres (Table 1). The specification for the [redacted] (CS-034-045) has been revised from that shown in the original NDA based on a discussion with Drs. Ahn and Shore of Biopharmaceutics on December 13, 1999.

In addition, Genentech makes a commitment to continue to work on development of an [redacted] that will provide a profile of the release of rhGH from the microspheres. A revised specification for either this new assay or the existing assay (CS-034-045) will be submitted within one year. This specification will include [redacted] with a [redacted] specification at the first and second timepoint, and a specification of not less than [redacted] of rhGH released at the last time point.

APPEARS THIS WAY
ON ORIGINAL

Redacted 1

pages of trade

secret and/or

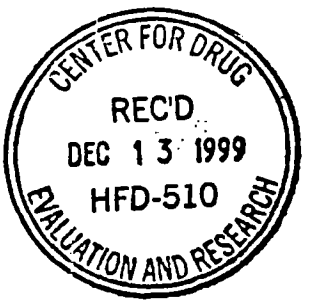
confidential

commercial

information

Genentech, Inc.

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



December 10, 1999

Solomon Sobel, M.D.,
Director
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 21-075** Nutropin Depot™
Amendment to a Pending Application
Item 2—Labeling
Item 6—Human Pharmacokinetics
Item 8—Clinical Section
Item 19—Other

Dear Dr. Sobel:

Genentech, Inc. is submitting the enclosed information to NDA 21-075 for Nutropin Depot [somatropin (rDNA origin) for injectable suspension]. For the record, we are submitting faxes which have been sent to the reviewers in response to their questions with respect to the above-listed Items, and copies of the iterations of the package insert which were discussed during the labeling negotiations. This submission also includes all product labeling (final package insert, final patient insert, vial labels, carton labels, and diluent labels).
A complete desk copy of all the items is provided in a black binder for Ms. Crystal King, P.D., M.G.A., Project Manager. The review copies have been placed in the appropriate colored binders.

An electronic archival copy of this submission on one CD has been submitted under separate cover to the CDER Central Document Room, according to the Guidance for Industry—Providing Regulatory Submissions in Electronic Format—General Considerations. Text is provided in Adobe Acrobat pdf format.

Note that in Item 2.B, colored text is used to represent the revisions made to the package insert; this colored text does not represent hyperlinks.

For help or information concerning any technical issues associated with the CD or electronic documents, please contact Mr. Scott Moore at (650) 225-7137 or Mr. Jan Van Gelder at (650) 225-1558. Please contact Ms. Fiona Cameron, Senior Manager, at (650) 225-1818, by fax at (650) 225-1397 or by email at cameron.fiona@gene.com if you have any other questions regarding the content of the application. We look forward to working with you during your review of this information.

Sincerely,

Roxanne Bates for RLG

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

APPEARS THIS WAY
ON ORIGINAL

Subject: Final Nutropin Depot Package Insert
Date: Thu, 09 Dec 1999 14:26:51 -0800
From: Fiona Cameron <cameron2@gene.com>
Organization: Genentech, Inc.
To: kingc@cder.fda.gov

Encrypted and Signed

Dear Crystal:

Attached are the following:

1. From GNE120999.doc - package insert showing today's revisions
2. FinalPI120999.doc - clean version of the final PI

Thanks for your help
Please let me know if you need anything else
Fiona

Subject: labeling!
Date: Thu, 09 Dec 1999 16:07:48 -0500 (EST)
From: "Crystal King 301-827-6423 FAX 301-443-9282" <KINGC@cder.fda.gov>
To: "Fiona Cameron" <cameron2@gene.COM>

Encrypted

and Signed

Fiona:
Saul and Rob have accepted the insertion of "injection site" for page 12, paragraph 2, 3rd line.

I look forward to your e-mail with the final draft label.
Thanks,
-Crystal

FinalPI120999.doc	**Name:** FinalPI120999.doc **Type:** Winword File (application/msword) **Encoding**

From GNE120999.doc	**Name:** From GNE120999.doc **Type:** Winword File (application/msword) **Encoding**

APPEARS THIS WAY
ON ORIGINAL

URGENT - PLEASE DELIVER TO DR. MALOZOWSKI IMMEDIATELY

Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.

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

To: Dr. Saul Malozowski, MD	To:
Fax: 301 443 9282	Fax:
Company: FDA	Company:
Dept: DMEDP	Dept:

From: Fiona Cameron, Regulatory Affairs
Tel: (650) 225-1818
Fax: (650) 225-1397
Date: 12/9/99
Number of Pages: 2 (including this one)

Reference: Nutropin Depot™ NDA 21-075

Dear Saul:

Regarding your question about the equal n analysis for the historical statement on growth rates in the PI. The data you requested is attached.

Best regards,

Fiona Cameron

Fiona Cameron

IMPORTANT CONFIDENTIALITY NOTICE
The documents accompanying this telecopy transmission contain confidential information belonging to Genentech which is legally protected. The information is intended only for the use of the individual or entity named below. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this telecopy information is strictly prohibited. If you have received this telecopy in error, please immediately notify us by telephone to arrange for return of the telecopied documents to us. Thank you.

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The table below shows the growth rates by year of treatment for the patients in the historical Genentech studies based on equal-n analyses (n=181).

Historical Studies of Daily GH in Naive, Prepubertal, GHD Children (Mean ± SD)

Source	Growth Rate (cm/yr) Year 1	Growth Rate (cm/yr) Year 2	Growth Rate (cm/yr) Year 3	Growth Rate (cm/yr) Year 4
NCGS Matched Analysis (n=69)	9.7 ± 2.3	8.1 ± 1.4	7.6 ± 1.8	6.8 ± 1.8
L0368g (n=48)	11.4 ± 2.7	8.9 ± 1.9	7.5 ± 2.0	n/a
87-072 (n=23)	11.4 ± 3.2	8.7 ± 2.0	7.8 ± 1.6	6.6 ± 2.1
87-070 (n=41)	10.8 ± 2.4	8.4 ± 1.7	7.7 ± 1.9	7.1 ± 2.0
Range	9.7 – 11.4	8.1 – 8.9	7.5 – 7.8	6.6 – 7.1

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ON ORIGINAL

Printed by Crystal King

Electronic Mail Message

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Date: 09-Dec-1999 10:45am
From: Fiona Cameron
cameron2@gene.com
Dept:
Tel No:

TO: kingc (kingc@A1)

Subject: FYI Minor Revisions to Carton Label

Dear Crystal:

Thanks for your emails. Last night when we were assembling the labeling to send to you on Friday, I realized that we have made a minor addition to the carton label that I wanted to draw your attention to. A pdf file is attached of one of the cartons so you can see what I mean. The change is as follows:

we added the words : "Single Use Vial" and "Discard Unused Portions" to emphasize these points for the users.

The text otherwise remains the same as originally submitted, with some of it having been moved to a different panel of the box in order to accomodate an "outsert" setup, ie where the PI is actually stuck to the outside of the box instead of being inside it. (We installed some new packaging equipment that does it this way, so that is why we made this change).

W[illegible]ll send you everything (ie all labels for all vial sizes and all t[illegible] I exchanges) on Friday. Can you estimate when we may receive the a[illegible]oval letter if everything goes according to plan?

Thanks!
Fiona

APPEARS THIS WAY
ON ORIGINAL

JA 21-075
Div File

Subject: Nutropin Depot Revised PI and Rationale
Date: Wed, 08 Dec 1999 18:19:30 -0800
From: Fiona Cameron <cameron2@gene.com>
Organization: Genentech, Inc.
To: kingc@cder.fda.gov

Encrypted and Signed

Dear Crystal:

I have revised the PI again based on our discussions today. We had an idea regarding the CT paragraph to make the historical comparison consistent with the naive paragraph comparison, and tried to get hold of you to discuss it, but unfortunately failed to get you.

So, I am attaching the revised PI, and a rationale document explaining what we did. Please let me know if we need a telecon to discuss this tomorrow. If not, I will send you the clean version tomorrow asap.

Thanks again for your help
Fiona

Rationale120899.doc	**Name:** Rationale120899.doc **Type:** Winword File (application/msword) **Encoding:**

v2From GNE120899.doc	**Name:** v2From GNE120899.doc **Type:** Winword File (application/msword) **Encoding:**

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ON ORIGINAL

Package Insert – Efficacy Section – CT Data Historical Context

Rationale for Change

As noted in discussions between FDA and Genentech on the historical comparisons for the naïve patients (p. 8 of PI), it is not appropriate to average values across clinical studies, which we did in our last version (12/8/99, first version) of the CT data section of the PI. We now propose displaying a range of growth rates across historical studies. To be consistent with the historical comparisons for naïve patients, we have also included the NCGS data and proposed the following sentence at the end of the last paragraph in the Efficacy Section:

> "Historical studies of GHD children treated with daily Protropin or Nutropin at a dose of 0.3 mg/kg weekly had the following mean values: first year growth rate [redacted] cm/yr; second year growth rate [redacted] cm/yr; third year growth rate [redacted] cm/yr; fourth year growth rate 6.6 to 7.1 cm/yr."

The data used for these mean values is derived from the same studies agreed upon for the historical comparisons for the first year growth rates in naïve patients (i.e., NCGS, L0368g, 87-072; 87-070, as shown in the table below). Note that there was an error in the previous correspondence of 12/6/99 that stated that the n of the NCGS dataset was [redacted] In fact, the n used in all NCGS analyses sent to FDA have used an n of 233). It was previously noted by FDA that determining a mean and SD across these data sets was not appropriate.

Since we are providing a range of mean values, it is not necessary to provide the total number of patients at each interval for the combined studies. We believe that this data represents a conservative presentation of all the demographically matched data from our studies. Overall, this revised wording provides the physician with the proper perspective to compare the performance of Nutropin Depot to daily injections of Protropin or Nutropin at the maximum dose in pediatric patients who are currently receiving daily GH therapy.

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ON ORIGINAL

Historical Studies of Daily GH in Naive, Prepubertal, GHD Children (Mean ± SD)

Source	Growth Rate (cm/yr) Year 1	Growth Rate (cm/yr) Year 2	Growth Rate (cm/yr) Year 3	Growth Rate (cm/yr) Year 4
NCGS Matched Analysis	10.1 ± 2.8 (n=233)	8.0 ± 1.7 (n=169)	7.6 ± 1.9 (n=118)	7.0 ± 2.0 (n=91)
L0368g	11.0 ± 2.9 (n=62)	8.8 ± 2.0 (n=56)	7.5 ± 2.0 (n=48)	n/a
87-072	11.3 ± 3.1 (n=31)	8.7 ± 2.1 (n=27)	7.7 ± 2.2 (n=25)	6.6 ± 2.1 (n=23)
87-070	10.9 ± 2.2 (n=55)	8.4 ± 2.1 (n=52)	7.7 ± 1.8 (n=47)	7.1 ± 2.0 (n=41)
Range	[redacted]	[redacted]	[redacted]	[redacted]

APPEARS THIS WAY
ON ORIGINAL

Subject: Revised PI and GH Graph
Date: Wed, 08 Dec 1999 11:51:35 -0800
From: Fiona Cameron <cameron2@gene.com>
Organization: Genentech, Inc.
To: kingc@cder.fda.gov

Hi Crystal

Attached are the revisions to the PI and also a revised GH graph, we will edit the title to include GH in the GH figure.

Talk to you soon
Thanks
Fiona

From GNE120899.doc	**Name:** From GNE120899.doc **Type:** Winword File (application/msword) **Encoding:** **Download Status:** Not downloaded with message

Revised GHplot120899.doc	**Name:** Revised GHplot120899.doc **Type:** Winword File (application/msword) **Encoding:** **Download Status:** Not downloaded with message

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ON ORIGINAL

This graph shows the median values for GH levels, as requested by Dr. Malozowski

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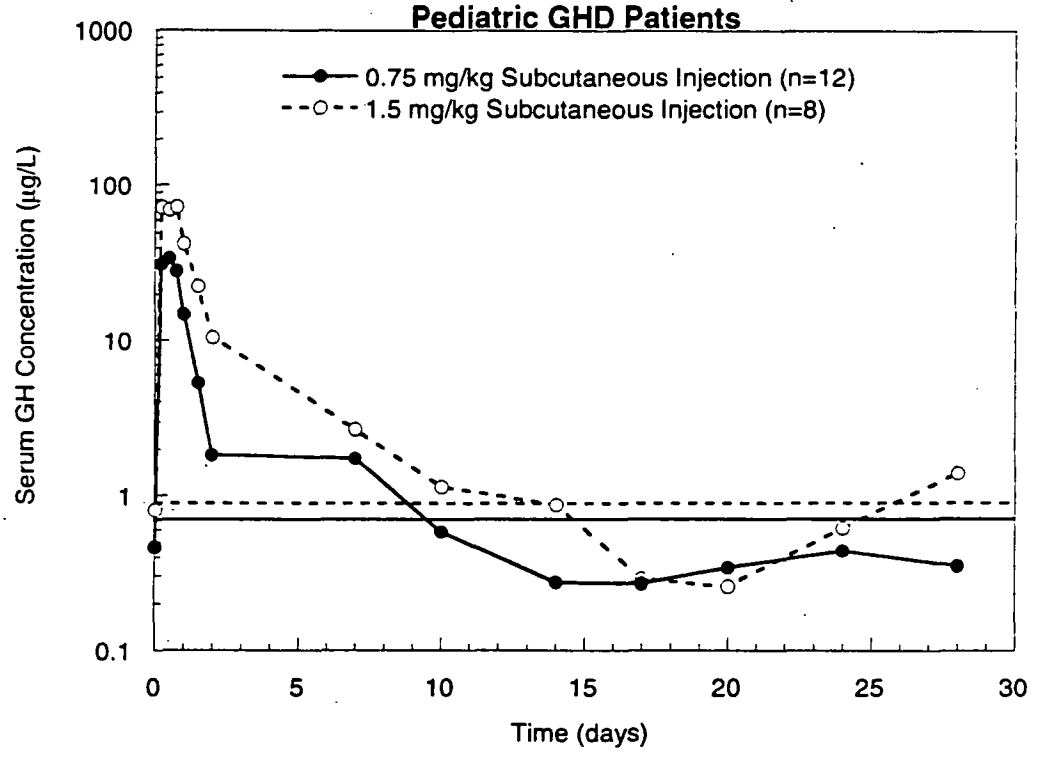
ON ORIGINAL

Figure 1
Single Dose Median Concentrations in Pediatric GHD Patients



APPEARS THIS WAY
ON ORIGINAL

Printed by Crystal King

Electronic Mail Message

Date: 07-Dec-1999 09:51pm
From: Fiona Cameron
cameron2@gene.com
Dept:
Tel No:

TO: kingc (kingc@A1)

Subject: More Information for Depot Call Wednesday

Dear Crystal:

Attached is a document which addresses the following issues, which we understand from Dr. Perlstein are among the items to be discussed tomorrow:

1. GH graph showing baselines

2. IGF-I graph - three versions provided, one with error bars shown

3. Response to Dr. Perlstein's conversation with Ken today.

If you could circulate this for review prior to our call, that would be great.

Thanks, again, for your help
Fiona

APPEARS THIS WAY
ON ORIGINAL

Package Insert – Inclusion of GH Figure with Baselines Shown

We propose to include the following figure in the PI showing GH profiles with baselines added as shown.

Draft

In order to obtain the baselines shown for each dose group, the median for each patient's baseline and predose values was calculated, and the median of those values was used. This was done in order to control for endogenous pulses of GH, which were variably present in some of the subjects at baseline and predose and had an inordinate effect on the mean values. Since the goal of adding this line is to assess the PK profile relative to the background of endogenous GH baseline levels, we feel the values calculated in this way are the most accurate.

APPEARS THIS WAY
ON ORIGINAL

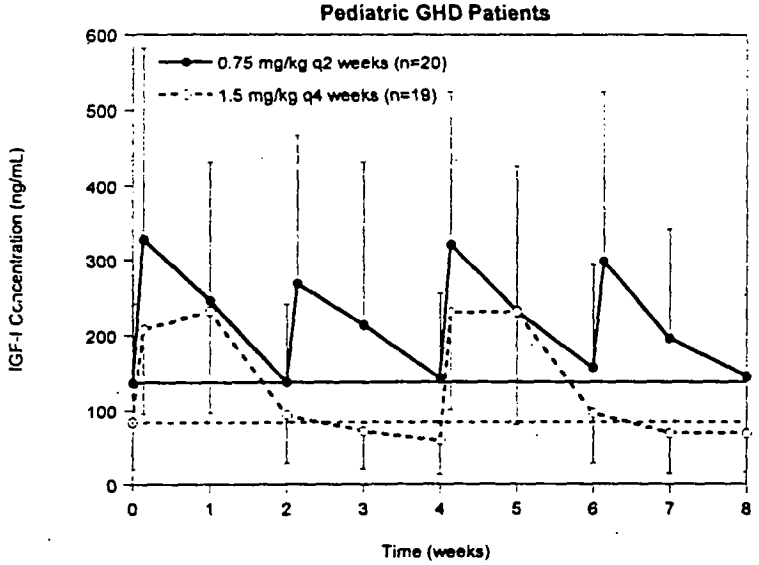
Package Insert – IGF-I Figure

Our preference would be to use a cosmetically improved version of the figure currently in the PI, as shown below:

Draft

However, if error bars are required, we would propose using the following graph:

Figure 2
Repeated-Dose Mean IGF-I Concentrations in Pediatric GHD Patients



We feel that a 4-week graph would fail to show the repeated dose effects in the once/month group. If the above figures are not acceptable, we would propose using the following graph from the NDA as a third option (with format improvements to be made):

Draft

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Package Insert – Efficacy

Regarding Dr. Perlstein's request that we add the range of previous treatment growth rate and growth rate on Depot to the sentence "Patients previously treated with daily GH for 2 or more years had a mean change in growth rate of –2.3 cm/yr", and correspondingly, that we add the beginning and ending growth rates for the respective years to the sentence "Historical studies of GHD children treated with daily Protropin or Nutropin at a dose of 0.3 mg/kg weekly had the following mean values for change in growth rate:[redacted]"

The CT patients (n=23) had a growth rate of 6.7 cm/yr on previous GH treatment, and a growth rate of 4.4 cm/yr on Depot. The table below shows the growth rates by year of treatment for the patients in the historical Genentech studies. It can be seen that the growth rates for the CT patients were less than those of the patients in the historical studies for patients treated for two or more years. In addition, we feel that the change in growth rate from year to year is more useful data for prescribing physicians, and for these reasons we feel that the sentences should remain as proposed by Genentech.

Historical Studies of Daily GH in Naive, Prepubertal, GHD Children

Source	ΔGrowth Rate (cm/yr) Year 1 → Year 2	ΔGrowth Rate (cm/yr) Year 2 → Year 3	ΔGrowth Rate (cm/yr) Year 3 → Year 4
L0368g	11.2 □8.8 -2.4 (n=56)	8.9 □7.5 -1.4 (n=48)	n/a
87-072	11.3 □8.7 -2.6 (n=27)	8.6 □7.7 -0.9 (n=25)	7.8 □6.6 -1.2 (n=23)
87-070	10.7 □8.3 -2.4 (n=57)	8.5 □7.6 -0.9 (n=50)	7.6 □7.1 -0.5 (n=42)
Weighted Mean (Range) of GNE Clinical Trials	11.0 □8.6 -2.4 (n=140) (-2.4 to -2.6)	8.7 □7.6 -1.1 (n=123) (-0.9 to -1.4)	7.7 □6.9 -0.7 (n=65) (-0.5 to -1.2)

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ON ORIGINAL

Printed by Crystal King

Electronic Mail Message

Date: 07-Dec-1999 08:56pm
From: Fiona Cameron
cameron2@gene.com
Dept:
Tel No:

TO: shorer (shorer@A1)

CC: kingc (kingc@A1)
Subject: Response to Request to Change Specification

Nutropin Depot
NDA 21-075

Dear Dr. Shore:

Attached is our response to your request that we change the specification on the [redacted] (Test Procedure CS-034-045) to a two part spec:

greater than or equal to [redacted] and
less than or equal to [redacted] in first [redacted] hours
and
greater than or equal to [redacted] at [redacted] hours.

We have made a proposal for a modified specification of:

[redacted]ater than or equal to [redacted] hours, and
[redacted]ter than or equal to [redacted] hours.

The attached document provides justification for our proposal.

We are scheduled to discuss the PI again tomorrow at 11.15 am your time. We could discuss this issue there, or afterwards. We look forward to talking with you.

Thanks for your help
Regards
Fiona

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Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.

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

To: Dwayne Keels	To:
Fax: 301 443 9282	Fax:
Company: FDA	Company:
Dept: DMEDP	Dept:

From: Fiona Cameron, Regulatory Affairs
Tel: (650) 225-1818
Fax: (650) 225-1397

Date: 12/6/99

Number of Pages: 20 (including this one)

Reference: Nutropin Depot™ NDA 21-075

Dear Mr. Keels:

Crystal King asked me to fax some documents to you for distribution to the team reviewing Genentech's Nutropin Depot NDA. I will also be emailing these documents to Crystal.

Attached are the following documents:

1. A short document describing Genentech's rationale for the changes we have made
2. Draft Package Insert showing Genentech's edits to the PI of 12/6/99

Thanks for your help. Please call me at (650) 225-1818 if you have any questions.

Best regards

Fiona Cameron

Fiona Cameron
cameron2@gene.com

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3 **Page(s) Redacted**

Draft

Labeling

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Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.

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

To: Joy Mele	To:
Fax: 301 443 9282	Fax:
Company: FDA	Company:
Dept: DMEDP, Biostatistics	Dept:

From: Fiona Cameron, Regulatory Affairs
Tel: (650) 225-1818
Fax: (650) 225-1397

Date: 12/6/99

Number of Pages: 2 (including this one)

Reference: Nutropin Depot™ NDA 21-075

Dear Joy:

Attached is a document showing which patients we used in our analysis of the CT data (n=23).

I hope that you find this helpful.Please call me at (650) 225-1818 if you have any questions.

Best regards

Fiona Cameron

Fiona Cameron
cameron2@gene.com

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DoseGrp	Subj#	Age	Yrs Treated	Pre GR	Mo-6 GR	•GR		Mean •GR
2	12011	10.7	0.9	11.9	7.2	-4.7		
2	12005	11.0	1	11.2	4.6	-6.7		
2	12004	10.0	1	10.1	6.5	-3.6		
1	8002	14.1	1.1	13.1	5.0	-8.1		
2	9006	4.5	1.2	11.0	5.4	-5.6		
1	12010	8.9	1.4	12.6	3.5	-9.1		
1	12008	9.7	1.4	8.8	4.3	-4.5	yr 1-->2	-6.0
2	10008	6.8	1.6	9.2	6.2	-3.0		
1	11001	10.3	1.8	5.1	7.9	2.8		
1	11003	7.9	1.8	4.0	9.6	5.6		
2	12002	10.7	2.1	7.5	5.7	-1.8	yr 2-->3	0.9
2	10010	10.2	2.7	7.5	3.1	-4.4		
2	7001	10.7	3.1	6.3	2.7	-3.5		
2	10007	4.3	3.1	7.8	4.8	-3.0		
1	2003	9.7	3.1	5.6	4.9	-0.7		
1	11006	10.1	3.2	3.2	9.3	6.0		
1	10003	10.3	3.4	7.0	4.2	-2.8		
1	12012	10.4	3.5	11.6	2.4	-9.2	yr 3-->4	-2.5
1	10005	8.5	4.7	5.9	2.9	-3.0		
1	12006	10.4	5.1	4.6	2.8	-1.8		
1	12007	9.4	5.2	7.9	3.7	-4.2		
2	12001	11.5	5.2	5.9	5.0	-0.9	yr 5-->6	-2.4
2	8003	13.0	6.1	6.0	5.6	-0.4		
	mean:	**9.7**	**2.8**	**8.0**	**5.1**	**-2.9**	**tx'd <2 yr**	**-3.7**
	sd:	**2.2**	**1.6**	**2.9**	**2.0**	**3.9**	**tx'd >2 yr**	**-2.3**
Subjects with inadequate follow-up data: 3005, 10002, 10006, 11007, 12009								

Printed by Crystal King

Electronic Mail Message

Date: 06-Dec-1999 06:21pm
From: Fiona Cameron
cameron2@gene.com
Dept:
Tel No:

TO: shorer (shorer@A1)

CC: kingc (kingc@A1)
Subject: Clarification requested on Spec Change Proposal

Dear Dr. Shore:

Thank you for the proposed spec change (to a two point spec) for the [redacted] I just wanted to confirm that your proposal is intended to replace the existing spec as it is written in the NDA. Please let me know.

We should be able to get back to you tomorrow (Tuesday) regarding the acceptability of your proposal.

Thanks again for your help
Regards
Fiona Cameron

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Electronic Mail Message

Date: 02-Dec-1999 10:01pm
From: Fiona Cameron
cameron2@gene.com
Dept:
Tel No:

TO: kingc (kingc@A1)

Subject: Revised Nutropin Depot PI

Dear Crystal:

Attached are the following documents for your review:

revised package insert
chart of historical GH studies
explanation of which studies were used for the historical comparison in the label.

Let me know when you would like to talk on Monday.

Thanks for your help and have a great weekend
Fiona

"WorldSecure Server <cder.fda.gov>" made the following annotations on 12/02/99 22:00:29

[INFO] -- Security Manager:
Message security properties:

Encrypted: Yes
Encryption: [redacted]
Signed by Sender: Yes
Contents Altered after signing: No
Signature Algorithm: SHA1

==========

Historical Studies of Daily GH in Naive, Prepubertal, GHD Children

Source	Baseline Age (yr)	Baseline Bone Age (cm/yr)	Max. Stim. GH (ng/mL)	GH Dose (mg/kg/wk)	Baseline Height SDS	Prestudy Growth Rate (cm/yr)	1st Year Growth Rate (cm/yr)	1st Year Change in Bone Age (yr)
Nutropin Depot Studies (n=69)	7.1± 2.8 (1.6 to 12.2)	5.7 ± 2.7 <10M, <9F	5.7 ± 2.8	n/a	-3.0 ± 1.0	5.1 ± 1.8	7.8 ± 1.9	1.0± 0.4
NCGS (matched analysis) (n=261)	7.8 ± 2.7 (3.1 to 12.2)	5.3 ± 2.4 <10M, <9F	5.3 ± 2.6	0.3	-3.1 ± 0.8	4.8 ± 2.6	10.1 ± 2.8	1.5 ± 1.0
L0368g (n=56)	8.0 ± 3.4 (0.9 to 15.2)	6.5 ± 3.1 <11M, <10F	4.8 ± 2.9	0.3	-2.7 ± 1.0	4.8 ± 2.3	11.2 ± 2.9	1.2 ± 0.6
87-072 (n=27)	9.2 ± 4.0 (0.7 to 20.4)	6.6 ± 3.2 <11M, <10F	4.9 ± 2.8	0.3	-2.8 ± 1.1	4.7 ± 3.4	11.3 ± 3.1	1.0 ± 0.5
87-070 (n=55)	8.8 ± 3.2 (2.5 to 14.1)	6.5 ± 3.0 <11M, <10F	5.1 ± 2.5	0.3	-3.0 ± 1.2	4.2 ± 1.7	10.9 ± 2.2	1.2 ± 0.5
86-061 (n=55)	7.8 ± 3.3 (1.6 to 14.5)	5.2 ± 2.9 <11M, <10F	3.7 ± 2.7	0.3	-3.1 ± 1.4	3.6 ± 1.7	9.8 ± 2.5	1.0 ± 0.4
Lilly SBA (n=41) 6-mo data	>2	<11M, <10F	n/a	0.18	n/a	3.5 ± 1.9	9.4 ± 2.1	n/a
Pharmacia SBA (n=180) avg. or range: 3 studies	(7.7 to 11.7)	<10M, <8F	<7; <10	0.19 - 0.27	-2.8 ± 1.2 to -3.1 ± 1.2	3.2 ± 2.1 to 3.7 ± 1.3	9.6	n/a
Novo SBA (n=11, 12-mo) (n=77, 6-mo)	10.8 (2.2 to 18.3)	n/a	n/a	0.18	-2.7	3.9	12 mo: 8.0 6 mo: 8.9	n/a
Serono SBA (n=16) 6-mo data	(1.3 to 19.2)	0.9 - 12.5	n/a	~0.18	n/a	3.8	10.6	1.1
BTG SBA (n=49) 6-mo data	11.0 (2.6 - 17.8)	n/a	<10	0.3 (TIW)	-3.4 ± 0.9	3.2 ± 1.9	9.6	n/a

Reference	Baseline Age (yr)	Baseline Bone Age (cm/yr)	Max. Stim. GH (ng/mL)	GH Dose (mg/kg/wk)	Baseline Height SDS	Prestudy Growth Rate (cm/yr)	1st Year Growth Rate (cm/yr)	1st Year Change in Bone Age (yr)
Albertsson-Wikland et al. 1988 (n=23)	2.2-13.3	BA Delay: 1.9 ± 1.4	n/a	0.27	-3.1 ± 1.5	4.0 ± 1.1	10.7 ± 2.3	1.1 ± 0.4
Angsusingha et al 1998 (n=30)	10.4 ± 3.2	7.4 ± 3.3	n/a	0.20	-2.9 ± 1.0	3.9 ± 1.1	8.2 ± 1.9	n/a
Pavia et al. 1992 (n=17)	6.4 ± 3.2 (1.6-11.6)	4.6 ± 2.9 (1.0-9.3)	3.9 ± 3.0	0.19	-3.5 ± 1.1	4.0 ± 1.5	10.1 ± 2.4	1.1 ± 0.5
Rasmussen et al. 1988 (n=107)	10.3 (1.5-18.3)	8.2 (0.3-15)	n/a	0.19	-2.7	4.1 ± 2.4	8.3 ± 2.5	n/a
Vassilopoulou-Sellin et al. 1995 (n=20) mn ± SE	12.1 (4.5-14.2)	11.0 (3.5-15.0)	<4.1 ng/ml in all but one case=6.8	0.30	n/a	3.3 ± 0.5	8.6 ± 0.6	n/a
Wilton et al. 1988 (n=99)	9.0 ± 3.6	6.4	n/a	0.12 - 0.31	-3.0 ± 1.2	3.4 ± 1.4	10.2 ± 2.5	n/a

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Notes Regarding Historical Studies Table

- The NCGS data are potentially the best match for the Nutropin Depot studies, since similar selection criteria were used, including bone age cutoffs. The population was limited to idiopathic GHD, since this was the diagnosis for over 90% of the Depot patients.

- As Dr. Perlstein noted, there was an analysis with approx. 2000 subjects from NCGS included in the NDA. This larger n was because it was not restricted to subjects with both 12-month growth rate and bone age change available. For this analysis, the 12-month growth rate was available for 1790 subjects and came to 9.9 ± 2.6 cm/yr. Change in bone age (n=340) was 1.4 ± 0.9 years.

- The 4 other Genentech clinical trials had identical inclusion criteria among them, however, the bone age cutoff was one year higher than the Depot studies. While this may have resulted in slightly older subjects, it also resulted in some subjects' entering puberty during the first year (hence, the reason for the lower cutoff in the more recent studies). These effects probably cancel each other out with respect to 1st year growth rate.

- The pivotal studies for the 5 other GH products approved in the U.S. used very similar inclusion criteria to the Genentech studies, although in some cases an older cohort was obtained. The doses used ranged from 0.18 to 0.30 mg/kg/week, which is consistent with the range of doses for which they are approved (0.16 - 0.30); Genentech's products are approved for "up to" 0.30 mg/kg/week.

- All of the above sources were restricted wherever possible to the subjects treated daily (6-7x/week), with the exception of the BTG study, which was TIW. In a few of the studies, it was not possible to tease out subjects who may have been treated TIW for some period of time. Since TIW dosing is in the current labeling for some of these products and is used by some physicians, this analysis remains relevant.

- In view of the fact that only 11 subjects were reported with 12 month data for Novo, we are willing to use the 6-month annualized growth rates for n=77 (i.e. 8.9 cm/yr), even though it is known that 6-month rates are generally greater than 12 month by approximately 1 cm/yr. Six month data was also used for Lilly, Serono, and BTG, making for a conservative analysis.

- The data from the MacGillivray paper were exclusively from study 87-072. The data which we have included for that study were derived from the final, verified report, on file at FDA. The data are very similar to that in the paper.

- While the 6 studies in the peer-reviewed literature are relevant with respect to inclusion criteria, with the exception of one or two, and the growth response ranged form 8.3 to 10.7 cm/yr, we are willing to exclude these from consideration per FDA's request for only rigorously monitored studies.

- Limiting the cohort to only the 10 sources containing pivotal studies leading to FDA approvals, the baseline characteristics are notable for the following slight differences as compared to the Depot studies: higher chron. age, greater bone age delay, lower max. stim. GH levels, and lower pretreatment growth rate. Although not in the chart, the studies also tended to have more organic subjects (e.g., 30% in L0368g). Taken in aggregate, these studies have more severe GHD subjects for whom greater responses to GH are expected. Thus, this would represent a conservative analysis with respect to comparisons with the Depot data.

Using the cohort defined above (10 sources used for FDA approvals), the sentence in the historical section becomes:

DRAFT

It is our opinion that these data accurately reflect reasonable, current expectations for daily GH therapy.

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Electronic Mail Message

Date: 01-Dec-1999 08:52pm
From: Fiona Cameron
cameron2@gene.com
Dept:
Tel No:

TO: kingc (kingc@A1)
TO: malozowskis (malozowskis@A1)

Subject: Information Regarding Number of Injections in Depot Trials

Dear Saul and Crystal:

Attached is a document which shows the number of injections administered to patients in the clinical trials 002 and 004. We have also shown how many injections these patients could have received using the to-be-marketed configurations, and also the minimum number of injections they could receive if they were allowed to choose a dose regimen.

I hope you find this helpful. We are working on the other changes you requested, and hope to have a modified version to you by the end of Thursday.

Please let me know if you would like a telephone call scheduled tomorrow (Thursday).

Thanks for your help
Best regards
Fiona

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Information Regarding Number of Injections

In response to Dr. Malozowski's question regarding the number of injections received by patients during the clinical studies, we are providing the following information.

- The weights of patients in studies [ ]03-002 and [ ]03-004, with both dose groups combined, were:

Weight Range (kg)	Number (%) Subjects
<15	36/91 (40%)
15-30	50/91 (55%)
30-45	5/91 (5%)

- The concentrations of rhGH used in the studies depended on the vial size and diluent volume, and included 13, 16, 19, and 22 mg/mL (all three vial sizes of the to-be-marketed product will be 19 mg/mL, per FDA request).

- Some subjects in the studies had changes in the number of injections/dose required based on the fact that their weight increased during study. Below we indicate the maximum number of injections/dose they needed in the study, i.e., based on their highest weight during the study. For comparison, we also show the number of vials needed per dose of the to-be-marketed product (assuming equal distribution of weights in the 2 dose groups).

	In Clinical Trials		With To-Be-Marketed Vials		
Max. No. Injections/ dose	1.5 1x/mo	0.75 2x/mo	1.5 1x/mo	0.75 2x/mo	Optimal Dose Regimen*
1	12/44 (27%)	41/47 (87%)	40%	95%	95%
2	28/44 (64%)	6/47 (13%)	55%	5%	5%
3	4/44 (9%)	0	5%	0	0

* to provide the fewest number of injections per dose, by using the twice monthly regimen for subjects over 15 kg.

Subject: 03-002 CT subjects - time on prev GH therapy
Date: Thu, 02 Dec 1999 08:42:34 -0800
From: Fiona Cameron <cameron2@gene.com>
Organization: Genentech, Inc.
To: mele@cder.fda.gov

Dear Joy:

Here is the information on the duration of previous treatment for the CT patients. I hope that you can read the .xpt file attached here.

Let me know if you have any problems with this.
Best regards
Fiona

Enclosed are items for Joy Mele. The raw data is in crt/datasets/03002/raw/endomet.xpt in the NDA. The variable collected was the date that growth hormone therapy was started. I calculated the years from the date growth hormone started to the first dosing date (number of days between/365.25). This matches what was originally presented in the 03-002 study report Appendix C Table 2.1. Please note that for 5 subjects only the month and year growth hormone was started were known. No substitution was made for the day in the report. However, to get the years for all subjects a day of 1 could be used.

The file prevgh_yrs.doc has the data definitions and a printout of the dataset created.

<<prevgh_yrs.doc>>

<<prvghyrs.xpt>>

Prvghyrs.xpt is a transport dataset with the raw data and the calculated results (for CT subjects only 38 records).

prevgh_yrs.doc	**Name:** prevgh_yrs.doc **Type:** Winword File (application/msword) **Encoding:** **Download Status:** Not downloaded with message

prvghyrs.xpt	**Name:** prvghyrs.xpt **Type:** unspecified type (application/octet-stream) **Encoding:** **Download Status:** Not downloaded with message

Currently Treated Subjects - Yrs on Prev GH Therapy

CONTENTS PROCEDURE

Data Set Name:	OUT002.PRGHYRS	Observations:	38
Member Type:	DATA	Variables:	9
Engine:	V612	Indexes:	0
Created:	10:41 Thursday, December 2, 1999	Observation Length:	73
Last Modified:	10:41 Thursday, December 2, 1999	Deleted Observations:	0
Protection:		Compressed:	NO
Data Set Type:		Sorted:	NO
Label:	CT Subjects - Yrs on Prev GH Therapy		

-----Engine/Host Dependent Information-----

Data Set Page Size:	8192
Number of Data Set Pages:	1
File Format:	607
First Data Page:	1
Max Obs per Page:	111
Obs in First Data Page:	38

-----Alphabetic List of Variables and Attributes-----

#	Variable	Type	Len	Pos	Format	Label
2	DATE	Num	8	8	DATE9.	First Dosing Date (from dosenda)
6	DGHBD	Num	8	41		GH start day
5	DGHBM	Num	8	33		GH start month
8	DGHBN	Num	8	57	DATE9.	GH start date: SAS date
7	DGHBY	Num	8	49		GH start year
4	DGRP_INT	Num	8	25	DGRPINTF.	Integrated dose group
9	PREVYRS	Num	8	65		Yrs on Prev GH Therapy
1	SPATIENT	Num	8	0		Site and Patient combined
3	STUDY	Char	9	16		Protocol number

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Currently Treated Subjects - Yrs on Prev GH Therapy

OBS	Site and Patient combined	First Dosing Date (from dosepda)	Protocol number	Integrated dose group	GH start month	GH start day	GH start year	GH start date: SAS date	Yrs on Prev GH Therapy
1	1001	15NOV1996	03-002	0.75q4	9	23	94	23SEP1994	2.14648
2	1002	15NOV1996	03-002	0.75q4	6	8	95	08JUN1995	1.44011
3	1003	15NOV1996	03-002	0.75q4	11	30	95	30NOV1995	0.96099
4	1004	15NOV1996	03-002	0.75q4	11	9	95	09NOV1995	1.01848
5	1005	20FEB1997	03-002	0.75q4	1	19	95	19JAN1995	2.08898
6	2001	11NOV1996	03-002	0.75q4	10	19	90	19OCT1990	6.06434
7	2002	11NOV1996	03-002	0.75q4	1	17	92	17JAN1992	4.81862
8	2003	05MAY1997	03-002	1.5q4 or 1.5 1x/Month	4	14	94	14APR1994	3.05818
9	3001	13FEB1997	03-002	0.75q4	2	8	91	08FEB1991	6.01506
10	3005	17APR1997	03-002	1.5q4 or 1.5 1x/Month	7	.	94	.	.
11	5002	05MAR1997	03-002	0.75q4	10	14	92	14OCT1992	4.38877
12	5003	05MAR1997	03-002	0.75q4	11	4	92	04NOV1992	4.33128
13	7001	28MAY1997	03-002	0.75q2 or 0.75 2x/Month	4	28	94	28APR1994	3.08282
14	8002	08MAY1997	03-002	1.5q4 or 1.5 1x/Month	4	15	96	15APR1996	1.06229
15	8003	28MAY1997	03-002	0.75q2 or 0.75 2x/Month	5	.	91	.	.
16	9006	12AUG1997	03-002	0.75q2 or 0.75 2x/Month	6	13	96	13JUN1996	1.16359
17	10002	17JUN1997	03-002	1.5q4 or 1.5 1x/Month	10	3	95	03OCT1995	1.70568
18	10003	22MAY1997	03-002	1.5q4 or 1.5 1x/Month	12	28	93	28DEC1993	3.39767
19	10005	20MAY1997	03-002	1.5q4 or 1.5 1x/Month	9	.	92	.	.
20	10006	22MAY1997	03-002	1.5q4 or 1.5 1x/Month	1	24	91	24JAN1991	6.32444
21	10007	20MAY1997	03-002	0.75q2 or 0.75 2x/Month	4	12	94	12APR1994	3.10472
22	10008	20MAY1997	03-002	0.75q2 or 0.75 2x/Month	10	2	95	02OCT1995	1.63176
23	10010	12AUG1997	03-002	0.75q2 or 0.75 2x/Month	11	18	94	18NOV1994	2.73238
24	11001	05MAR1997	03-002	1.5q4 or 1.5 1x/Month	5	6	95	06MAY1995	1.83162
25	11003	05MAR1997	03-002	1.5q4 or 1.5 1x/Month	5	.	95	.	.
26	11006	16JUL1997	03-002	1.5q4 or 1.5 1x/Month	5	6	94	06MAY1994	3.19507
27	11007	20AUG1997	03-002	1.5q4 or 1.5 1x/Month	.	.	.	.	.
28	12001	01OCT1997	03-002	0.75q2 or 0.75 2x/Month	7	15	92	15JUL1992	5.21287
29	12002	01OCT1997	03-002	0.75q2 or 0.75 2x/Month	9	5	95	05SEP1995	2.07255
30	12004	01OCT1997	03-002	0.75q2 or 0.75 2x/Month	10	2	96	02OCT1996	0.99658
31	12005	01OCT1997	03-002	0.75q2 or 0.75 2x/Month	9	25	96	25SEP1996	1.01574
32	12006	08OCT1997	03-002	1.5q4 or 1.5 1x/Month	8	21	92	21AUG1992	5.13073
33	12007	08OCT1997	03-002	1.5q4 or 1.5 1x/Month	7	29	92	29JUL1992	5.19370
34	12008	08OCT1997	03-002	1.5q4 or 1.5 1x/Month	5	1	96	01MAY1996	1.43737
35	12009	01OCT1997	03-002	1.5q4 or 1.5 1x/Month	2	19	95	19FEB1995	2.61465
36	12010	21OCT1997	03-002	1.5q4 or 1.5 1x/Month	5	22	96	22MAY1996	1.41547
37	12011	21OCT1997	03-002	0.75q2 or 0.75 2x/Month	12	11	96	11DEC1996	0.85969
38	12012	21OCT1997	03-002	1.5q4 or 1.5 1x/Month	4	6	94	06APR1994	3.54278

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Printed by Crystal King

Electronic Mail Message

Date: 30-Nov-1999 10:18pm
From: Fiona Cameron
cameron2@gene.com
Dept:
Tel No:

TO: kingc (kingc@A1)

Subject: Revisions to Nutropin Depot Package Insert

Dear Crystal:

I will try to catch you by phone tomorrow to confirm that we are still scheduled to have a call with you at 2pm your time. Please send me an email or voicemail regarding this if I do not catch you. Attached for your review are the following documents:

1. Revised Package Insert. I "accepted" all the changes that we agreed on, and removed deleted ones which we agreed should be deleted, in order to have a cleaner document to work from. I left in strikeout text which we all agreed that Genentech should propose a rewrite for.

2. Rationale document supporting our most recent changes

3. Revisions to the Patient Insert. As I mentioned previously, we did make some minor changes for consistency, and also edited Dr. Perlstein's suggested text a little.

will see that we added a statement to the package insert regarding range of growth rates seen in historical GH studies. The rationale ument provides more detail on the supporting information for this statement. In addition, we also fedexed a hard copy of the relevant references to Dr. Perlstein's attention tonight, so he should receive those first thing tomorrow morning (ie Wednesday).

Hope things are OK with you.
Thanks so much for your help
Fiona

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

6 **Page(s) Redacted**

Draft

Labeling

Genentech, Inc.

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

APPEARS THIS WAY
ON ORIGINAL

November 30, 1999

Robert Perlstein, M.D.
Medical Officer
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
5600 Fishers Lane
Rockville, MD 20857

Subject: **Nutropin Depot™ NDA 21-075**
Desk Copy of References Supporting Historical Growth Rates

Dear Dr. Perlstein:

Further to our discussions regarding the package insert, we are providing the enclosed references and publications which support our statement regarding historical growth rates for your convenience.

Please do not hesitate to contact me at (650) 225-1818, by fax at (650) 225-1397 or by email at cameron.fiona@gene.com if you have any further questions.

Sincerely,

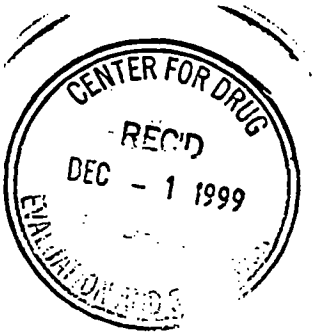
Fiona Cameron

Fiona Cameron
Senior Manager
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Genentech, Inc.

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



November 30, 1999

Solomon Sobel, M.D.,
Director
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 21-075** Nutropin Depot™
Amendment to a Pending Application
Item 4—Chemistry, Manufacturing and Controls
Item 6—Human Pharmacokinetics
Item 8—Clinical

Dear Dr. Sobel:

Genentech, Inc. is submitting the enclosed information to NDA 21-075 for Nutropin Depot [somatropin (rDNA origin) for injectable suspension]. For the record, we are submitting faxes that have been sent to the reviewers in response to their questions regarding Items 4, 6, and 8 of the application. In addition, we are also including responses to questions received on November 19, 1999 regarding the Chemistry, Manufacturing and Controls section of the NDA, and an update to the Stability section of the NDA. A complete desk copy of all the items is provided in a black binder for Ms. Crystal King, P.D., M.G.A., Project Manager. The review copies have been placed in the appropriate colored binders. Field copies of the Chemistry information have also been submitted to the San Francisco and Boston District offices.

Certification of Substantial Financial Support of Clinical Studies

Further to an inquiry by Ms. Crystal King, we hereby certify that Genentech, Inc. provided substantial financial support for the Nutropin Depot studies [redacted]03-001,

[redacted]03-002, [redacted]03-003, and [redacted]03-004. Genentech paid 100% of the cost of the studies, which were performed under contract by [redacted]

Stability Update

The stability update provides for the following dating periods for the various intermediates and drug product:

Intermediate/Product	Storage Conditions	Expiration Dating
rhGH Bulk Drug Substance in Bicarbonate Formulation	[redacted]	[redacted]
rhGH-Zinc Acetate Powder		
ProLease rhGH Bulk Microspheres		
Nutropin Depot Final Product	2°C–8°C	

An electronic archival copy of this submission on one CD has been submitted under separate cover to the CDER Central Document Room, according to the Guidance for Industry—Providing Regulatory Submissions in Electronic Format—General Considerations. Text is provided in Adobe Acrobat pdf format.

For help or information concerning any technical issues associated with the CD or electronic documents, please contact Mr. Scott Moore at (650) 225-7137 or Mr. Jan Van Gelder at (650) 225-1558. Please contact Mr. Art Blum, Director, at (650) 225-1559 if you have any questions regarding the Chemistry information. Please contact Ms. Fiona Cameron, Senior Manager, at (650) 225-1818, by fax at (650) 225-1397 or by email at cameron.fiona@gene.com if you have any other questions regarding the content of the application. We look forward to working with you during your review of this update.

Sincerely,

Roxanne Bates for RLG

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

APPEARS THIS WAY
ON ORIGINAL

21075-016 sub initials

Subject: Nutropin Depot - Revised PI
Date: Wed, 24 Nov 1999 08:22:53 -0800
From: Fiona Cameron <cameron2@gene.com>
Organization: Genentech, Inc.
To: kingc@cder.fda.gov

Encrypted and Signed

Hi Crystal:

Attached for your use are electronic versions of the following:

revised package insert (we used your previous version, and added our changes, so it gets a bit confusing to look at, however you can of course show or print it with the strikeouts etc turned off to see the clean version)

the document which gives our reasons for why we made certain changes

I also faxed the above items to Dwayne Keels on Tuesday night.

As we discussed, I'll wait for your call (to 650 225 1818, my usual #) on Monday after your meeting, but I am going to have the folks standing by anyway, just in case you are ready to talk.

Hopefully this came across encrypted and signed ok, I worked a little with Shana Johnson on Wednesday and she says we should be all set. Let me know if anything looks out of the ordinary on this front.

Hope you had a great Thanksgiving
Best regards
Fiona

FromGNE112399.doc	**Name:** FromGNE112399.doc **Type:** Winword File (application/msword) **Encoding:**

Rationale1123.doc	**Name:** Rationale1123.doc **Type:** Winword File (application/msword) **Encoding:**

APPEARS THIS WAY
ON ORIGINAL

King

Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.

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

To: Dwayne Keels	To:
Fax: 301 443 9282	Fax:
Company: FDA	Company:
Dept: DMEDP	Dept:

From: Fiona Cameron, Regulatory Affairs
Tel: (650) 225-1818
Fax: (650) 225-1397

Date: 11/23/99

Number of Pages: (including this one)

Reference: Nutropin Depot™ NDA 21-075

Dear Mr. Keels:

Crystal King asked me to fax some documents to you for distribution to the team reviewing Genentech's Nutropin Depot NDA. I will also be emailing these documents to Crystal.

Attached are the following documents:

1. A short document describing Genentech's rationale for the changes we have made
2. Draft Package Insert showing Genentech's edits to the FDA's draft of 11/18/99.
3. A clean version of the above document, showing how it looks without the strikeouts and underlines being shown

Thanks for your help. Please call me at (650) 225-1818 if you have any questions.

Best regards

Fiona Cameron

Fiona Cameron
cameron2@gene.com

IMPORTANT CONFIDENTIALITY NOTICE

The documents accompanying this telecopy transmission contain confidential information belonging to Genentech which is legally protected. The information is intended only for the use of the individual or entity named below. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this telecopy information is strictly prohibited. If you have received this telecopy in error, please immediately notify us by telephone to arrange for return of the telecopied documents to us. Thank you.

11/23/99

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Dear Crystal:

We have provided our rationale for the changes we made to the version of the Depot package insert that we received from you on 11/18/99 below for your consideration. These points were discussed during our recent call, but we thought it might be useful to provide them in writing for the use of the review team.

I hope you find this helpful. Thanks to you and the review team for your time, and we look forward to talking with you again on Monday, or if that is not possible, Wednesday, as we discussed.

Thanks as always for your assistance.
Best regards

Fiona Cameron

Fiona Cameron
Senior Manager
Regulatory Affairs
Genentech, Inc.

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Indication and CT Data (page 9 of package insert version showing strikeouts)

No currently treated (CT) patients were included in the Phase III study per our agreement with FDA at the pre-Phase III meeting. It was understood that this would not result in a restriction on the label. This is similar to the case with most other GH products, for which data in naïve subjects has been utilized to support use without restrictions. As we discussed during the teleconference on 11/22/99, the FDA's wording would unfortunately be interpreted as a contraindication for the purposes of reimbursement, which appears not to be the intention of FDA. CT patients were studied in Phase I/II for pharmacokinetics and safety, and no unique or unexpected safety signals were seen in this population. Therefore, CT patients should not be specifically excluded from the indication. However, we agree that physicians should be aware that the data in CT patients was limited, so we have added a statement to the indication regarding the limited experience in this population.

We have added a similar sentence to the efficacy section to show that experience in CT patients is limited. Since no CT subjects were studied in the pivotal phase III study, it would be inappropriate to include specific efficacy data for this population. The Phase I/II trial, which contained a small number of CT patients at three dose regimens, was designed and powered to assess PK, safety and tolerability, not efficacy. The CT patients varied considerably with respect to previous treatment duration (0.9 to 6.3 years) and GH dose. These factors have a profound effect on growth rate in subjects on daily GH and would be expected to have an impact on comparative growth rates of patients changing therapies. Considering the heterogeneity and low number of CT patients, definitive conclusions cannot be drawn regarding efficacy.

We have also reinstated "endogenous GH secretion" to the indication statement, as this is consistent with the labeling of our other growth hormone products.

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ON ORIGINAL

Comparative Efficacy (page 8)

At the pre-Phase III meeting with FDA, it was agreed that there would be no daily GH arm in the Phase III study and, additionally, that no formal comparisons with historical GH studies would be made. The protocol for the pivotal Phase III efficacy study did not specify any comparison to Nutropin AQ study L0368g or other historical data.

Because of different baseline characteristics, as well as other known shortcomings of historical controls, formal statistical comparisons of Depot versus historical daily GH studies are difficult to interpret and may be misleading.

Per our pre-Phase III and pre-NDA meetings with FDA, we have agreed to include the efficacy data for Nutropin Depot so that physicians are made aware of the efficacy outcomes for the studies. This is in marked distinction to other GH products marketed in the U.S., for which no efficacy data for pediatric GHD are included in the label. Some of these other labels recommend lower doses, which have been shown to result in lower growth rates than are seen with other dosing regimens.

The appropriate context in which to evaluate the growth rate is with respect to the rate of bone age advancement, which optimally is commensurate with the growth rate. Appropriate bone age advancement assures that ultimate growth potential has been preserved, which is what we have observed in the Nutropin Depot studies.

Discontinuation Statement (page 9)

Since discontinuation due to dissatisfaction with growth rate is a subjective decision made by physicians/patients, we feel that it is not appropriate to present this information in the PI. It would also be inappropriate to include such data because patients were not followed on daily GH after they discontinued Depot therapy. Therefore, data does not exist to suggest that the growth response in these patients would have changed upon treatment with daily GH at the currently approved dosages. We believe physicians are better served by providing them with actual growth data that they can use to determine which patients they would consider discontinuing from therapy.

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Monitoring Statement in Indications Section (page 10)

The statements regarding use by experienced physicians and assessment of patients who respond poorly are already present in the PI under Precautions and Dosage and Administration, respectively. In addition, it is noteworthy that the lower end of the range of growth rates in the Phase III Depot study is similar to that observed with daily GH. While we agree that the distribution is somewhat different for Depot, it is not readily possible to determine if an individual patient is not responding to Depot or to GH therapy in general. There are also no data to substantiate that a patient would have significantly improved growth rate if switched to daily GH. Based on data for naïve subjects who have continued on Depot therapy, there has been good maintenance of growth rates with waning similar in magnitude to daily GH; thus, the second warning regarding waning is not warranted.

Adverse Reactions (pages 13, 14 & 15)

In order to avoid confusion, we suggest including only percentages of injections for injection site reactions. Incidence per injection provides a clear representation of the likelihood of experiencing an injection site adverse reaction to an individual injection. We have provided alternative wording for this section.

We agree that percentages of subjects should be included on all other adverse reactions cited. However, adding up percentages for several different and possibly unrelated adverse reactions (headache, nausea, fever and vomiting) is not clinically meaningful in determining incidence and could be confusing to physicians. We have provided individual percentages instead, as is the usual practice.

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The label already has a statement describing the initial rapid release of Nutropin Depot in the PK section. The graph (which has been revised per FDA's request to show the high end better) adequately illustrates the initial release of GH in the two dose groups. Inclusion of fractional AUCs may be misinterpreted by a reader as percentage of drug released, and therefore we have excluded these numbers in the PI.

We have included a wider range of estimates of bioavailability as per our discussion. We feel that giving a narrow range suggests that the data is more accurate than it really is, based on the limitations of the available data for daily GH. The statement regarding bioavailability after the second day of dosing is misleading as written and fails to communicate the amount of GH actually released during days 2-14, which although less than daily GH, is in a safe and effective range, as illustrated by the IGF-I response over the first 16-20 days.

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ON ORIGINAL

NDA 21-075 AMENDMENT
BZ

Genentech, Inc.

ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 26 1999
CDR

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

October 22, 1999

Solomon Sobel, M.D.,
Director
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

Subject: **NDA 21-075** Nutropin Depot™
Amendment to a Pending Application
Item 2—Labeling
Item 4—Chemistry, Manufacturing and Controls
Item 6—Human Pharmacokinetics
Item 8—Clinical Section

Dear Dr. Sobel:

Genentech, Inc. is submitting the enclosed information to NDA 21-075 for Nutropin Depot [somatropin (rDNA origin) for injectable suspension]. For the record, we are submitting faxes that have been sent to the reviewers in response to their questions. In addition, we are also including an amendment to the Chemistry, Manufacturing, and Controls section which provides new information regarding the validation of the [redacted] as well as correcting some information in the original NDA. A complete desk copy of all the items is provided in a black binder for Ms. Crystal King, Project Manager. The review copies have been placed in the appropriate colored binders. Field copies of the Chemistry information have also been submitted to the San Francisco and Boston District offices.

An electronic archival copy of this submission on one CD has been submitted under separate cover to the CDER Central Document Room, according to the Guidance for Industry—Providing Regulatory Submissions in Electronic

Format—General Considerations. Text is provided in Adobe Acrobat pdf format. At the request of Dr. R. Shore, this electronic copy also includes a Word version of the proposed package insert for Nutropin Depot, which has been edited to show which information was previously approved for Nutropin [somatropin (rDNA origin) for injection] under NDA 19-676. This Word version is contained in the folder designated for Item 6, hpbio.

For help or information concerning any technical issues associated with the CD or electronic documents, please contact Mr. Scott Moore at (650) 225-7137 or Mr. Jan Van Gelder at (650) 225-1558. Please contact Mr. Art Blum, Director at (650) 225-1559 if you have any questions regarding the Chemistry information. Please contact Ms. Fiona Cameron, Senior Manager at (650) 225-1818, by fax at (650) 225-1397 or by email at cameron.fiona@gene.com if you have any other questions regarding the content of the application. We look forward to working with you during your review of this update.

Sincerely,

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

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X4.1a

Genentech, Inc.

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(650) 225-1000
FAX: (650) 225-6000

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
OCT. 13 1999
HFD-510

ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 12 1999
CDR

October 8, 1999

Solomon Sobel, M.D.,
Director
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 21-075** Nutropin Depot™
Amendment to a Pending Application
Item 9—Safety Update

Dear Dr. Sobel:

Per 21 CFR 314.50 we are submitting this Safety Update to Nutropin Depot NDA 21-075. This Safety Update contains safety information collected during the period June 1, 1998 to June 3, 1999 from the ongoing extension study, [redacted]03-003. Updated tables and listings that contain all consolidated data from both the [redacted]03-003 interim study report and the safety update period are provided in Appendices A and B. In addition, the following data is presented in Appendix A for the duration of the update period only: subject disposition, extent of exposure, and adverse events.

This submission does not contain revised labeling, as the safety data collected during the update period is consistent with that seen earlier during the clinical trials and with the current draft labeling.

An electronic archival copy of this submission on one CD has been submitted under separate cover to the CDER Central Document Room, according to the Guidance for Industry—Providing Regulatory Submissions in Electronic Format—General Considerations. Text is provided in Adobe Acrobat pdf format. No datasets are being supplied with this Update. The patient listings contained

in Appendix B and the case report forms contained in Item 12 are provided in electronic form only.

For help or information concerning any technical issues associated with the CD or electronic documents, please contact Mr. Scott Moore at (650) 225-7137 or Mr. Jan Van Gelder at (650) 225-1558. Please contact Ms. Fiona Cameron, Senior Manager, at (650) 225-1818, by fax at (650) 225-1397, or by email at cameron.fiona@gene.com if you have any general questions regarding the content of the application. We look forward to working with you during your review of this update.

Sincerely,

Roxane Bales for RLG

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

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ON ORIGINAL

REVIEWS COMPLETED

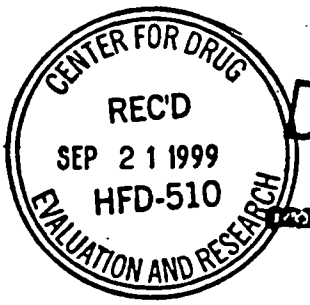
CSO ACTION:
☐ LETTER ☐ E-MAIL ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

Genentech, Inc.

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



DUPLICATE

BLL

September 20, 1999

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

Subject: **NDA 21-075**, Nutropin Depot™
Amendment to a Pending Application
12-Month Efficacy Update

Dear Dr. Sobel:

Further to a request by Dr. Saul Malozowski of your office, we are submitting new 12-month efficacy information to our pending New Drug Application for Nutropin Depot™ [somatropin (rDNA origin) for injectable suspension].

As agreed with Dr. Malozowski, Dr. Perlstein, Ms. Mele and Ms. King, this efficacy update contains information on 69 naïve patients who have been treated for a total of 12 months with the two dose regimens used in the pivotal trial [redacted]03-004. In addition, the SAS datasets provided with this submission include data for an additional 13 patients who were treated with growth hormone prior to Nutropin Depot administration, and 5 patients who initially received a lower dose than those used in the pivotal trial.

This submission contains revised labeling. The package insert has been updated to reflect the new 12-month efficacy information.

An electronic archival copy of this submission on one CD has been submitted under separate cover to the CDER Central Document Room, according to the Guidance for Industry – Providing Regulatory Submissions in Electronic

Format - General Considerations. Text is provided in Adobe Acrobat pdf format, and SAS datasets are supplied as SAS Transport files.

A desk copy containing hard copies of the SAS documentation has been sent directly to Ms. Joy Mele.

For help or information concerning any technical issues associated with the CDs or electronic documents, please contact Mr. Scott Moore at (650) 225-7137 or Mr. Jan Van Gelder at (650) 225 1558. Please contact Ms. Fiona Cameron, Senior Manager, at (650) 225-1818, by fax at (650) 225-1397 or by email at cameron.fiona@gene.com if you have any general questions regarding the content of the application. We look forward to working with you during your review of this update.

Sincerely,

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

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SUPPL NEW CORRESPONDENCE
SAC 135

nentech, Inc.

Way
an Francisco, CA 94080-4990
5-1000
0) 225-6000

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 17 1999
HFD-510

August 13, 1999

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

Subject: **NDA 21-075**
Nutropin Depot™ [somatropin (rDNA origin) for injectable suspension]
Amendment: Response to Request for Information

Dear Dr. Sobel:

Reference is made to our New Drug Application, NDA 21-075 for Nutropin Depot™ [somatropin (rDNA origin) for injectable suspension], submitted on June 25, 1999, for the long-term treatment of patients with growth failure due to a lack of endogenous growth hormone secretion.

As requested during a telephone conversation held on August 10, 1999 with Ms. Joy Mele of your Division, Mr. Shawn McLaughlin and Dr. Ken Attie of Genentech, we are submitting additional information consisting of a memo describing the randomization procedures used in the Phase III Study [redacted]03-004). This information was sent by facsimile to Ms. Joy Mele on August 11, 1999.

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

Sincerely,

Allen D. Roses for

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

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ [illegible] ☐ MEMO
CSO INITIALS DATE

21075-008 sub ss

Genentech, Inc.

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

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 21-075**
Nutropin Depot™ [somatropin (rDNA origin) for injectable suspension]
Request for Waiver of Requirement to Conduct Pediatric Studies
[21CFR 201.23(a)]

Dear Dr. Sobel:

Reference is made to our New Drug Application, NDA 21-075 for Nutropin Depot™ [somatropin (rDNA origin) for injectable suspension], submitted on June 25, 1999 for the long-term treatment of patients with growth failure due to a lack of endogenous growth hormone secretion.

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 Depot. The studies already performed would be [redacted]03-002, [redacted]03-003, and [redacted]03-004, for pediatric growth hormone deficiency, contained in NDA 21-075.

21075-007 sub ss

APPEARS THIS WAY
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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

APPEARS THIS WAY
ON ORIGINAL

21075-007 sub ss

Genentech, Inc.

1 DNA Way
South San Francisco, CA 94080-4990
(650) 225-1000
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June 25, 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: **Original NDA 21-075**
Nutropin Depot™ [somatropin (rDNA origin) for injectable suspension]
User Fee ID Number 3742

Dear Dr. Sobel:

Genentech, Inc. is pleased to submit an original New Drug Application for Nutropin Depot™[somatropin (rDNA origin) for injectable suspension], a sustained-release formulation of recombinant human growth hormone, indicated for the long-term treatment of patients with growth failure due to a lack of endogenous growth hormone secretion.

This product, previously referred to as [redacted]rhGH, was developed in conjunction with [redacted] under their IND [redacted] manufactures and fills the drug product, and [redacted] manufactures and fills the diluent. [redacted] acts as a contract manufacturer for Genentech. Chemistry, manufacturing and controls information for [redacted] operations are contained in this application, and cross-reference is made to Drug Master Files [redacted] and [redacted] which describe the manufacture of the diluent and [redacted] facilities, respectively. Appropriate letters of authorization permitting the Agency to cross-reference the [redacted] IND and the Master Files are included in this application. Genentech is responsible for the drug substance manufacture, for the labeling, packaging, distribution, and marketing of the final product, and for adverse event reporting.

This NDA also makes reference to the following Genentech NDAs: Nutropin® NDAs 19-676, 20-168 and 20-656, Nutropin AQ® NDA 20-522, and Protropin® NDA 19-107.

This NDA consists of 30 volumes assembled according to the Guideline on Formatting, Assembling and Submitting New Drug Applications, and one archival copy in electronic format. The required number of review copies (including a Microbiology volume, and two copies of two Methods Validation Volumes compiled for use by the laboratory) in hard copy are also provided. The attached document, Electronic Submission Documentation, describes the pagination and volume system for the paper copies, as well as key elements of the electronic submission.

Application Fee and Claimed Exclusivity
An application fee of $[redacted] has been remitted to [redacted] Bank.

At this time, since this application contains reports of new clinical investigations sponsored by Genentech which are essential to the approval of the NDA, we are claiming three years of exclusivity. However, we have applied for designation of Nutropin Depot as an orphan drug product (application reference number [redacted]). If this designation is subsequently granted, we will then claim seven-year exclusivity for this product and apply for a refund of the application fee, per 736(a)(1)(E) of the Food, Drug and Cosmetic Act.

Electronic NDA
An electronic archival copy of this NDA on 2 CDs has been submitted under separate cover to the CDER Central Document Room according to the Guidance for Industry - Providing Regulatory Submissions in Electronic Format – General Considerations. Text is provided in Adobe Acrobat pdf format, and SAS datasets are supplied as SAS Transport files. The CDs contain 1.05 GB.

All sections of the NDA are provided in electronic format. The following parts are only provided electronically, and are not contained in the paper review copies:

- all publications (references)
- investigators' curricula vitae
- Item 11 – Case Report Tabulations

- Item 12 – Case Report Forms
- Subject Data Listings
- Subject Laboratory Data

Genentech personnel are available as needed to provide training and/or answer questions on the use of the electronic submission.

Safety and Stability Updates
We anticipate filing a safety update (for the ongoing study [redacted]03-003) in October 1999, and a stability update in December 1999.

Study Site Audits
Information regarding the Phase III clinical trial sites has been sent to Dr. H.W. Ju of the Division of Scientific Investigation as requested.

Field Copies
Field copies of the Chemistry, Manufacturing and Controls section have been sent to both Genentech's district FDA office (San Francisco District), and to [redacted]district FDA office[redacted]

Contacts
For any questions regarding the Chemistry, Manufacturing and Controls section of this application, please contact Mr. Art Blum, Director, Regulatory Affairs at (650) 225-1559 or by fax at (650) 225-4171.

For all other questions, please contact Ms. Fiona Cameron, Senior Manager, Regulatory Affairs at (650) 225-1818, or by fax at (650) 225-1397.

We look forward to working closely with the Agency during the review of this application. Please do not hesitate to contact the individuals identified above if you have any questions or require any further information.

Sincerely,

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

APPEARS THIS WAY
ON ORIGINAL

21075-006 sub ss

BEST POSSIBLE COPY

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
Genentech, Inc.

DATE OF SUBMISSION
June 25, 1999

TELEPHONE NO. *(Include Area Code)*
(650) 225-1202

FACSIMILE (FAX) Number *(Include Area Code)*
(650) 225-1397

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
1 DNA Way
South San Francisco, California, USA 94080-4990
License 1048

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE*
N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) **21-075**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
somatropin (rDNA origin) for injectable suspension

PROPRIETARY NAME *(trade name)* IF ANY
Nutropin Depot

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
N/A

CODE NAME *(If any)*
ProLease rhGH

DOSAGE FORM:
injectable suspension

STRENGTHS:
13.5mg,18.0mg, 22.5mg

ROUTE OF ADMINISTRATION:
subcutaneous

(PROPOSED) INDICATION(S) FOR USE:
Long-term treatment of growth failure due to a lack of adequate endogenous growth hormone secretion

APPLICATION INFORMATION

APPLICATION TYPE (check one)
■ NEW DRUG APPLICATION (21 CFR 314.50) □ ABBREVIATED APPLICATION (ANDA, AADA, 21CFR 314.94)
□ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ■ 505 (b) (1) □ 505 (b) (2) □ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
■ ORIGINAL APPLICATION □ AMENDMENT TO A PENDING APPLICATION □ RESUBMISSION
□ PRESUBMISSION □ ANNUAL REPORT □ ESTABLISHMENT DESCRIPTION SUPPLEMENT □ SUPAC SUPPLEMENT
□ EFFICACY SUPPLEMENT □ LABELING SUPPLEMENT □ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT □ OTHER

REASON FOR SUBMISSION
new marketing application

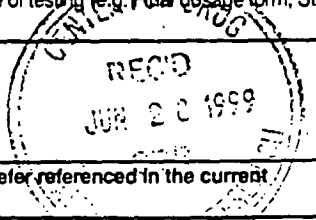
PROPOSED MARKETING STATUS (check one) ■ PRESCRIPTION PRODUCT (Rx) □ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED **30** THIS APPLICATION IS □ PAPER ■ PAPER AND ELECTRONIC □ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please refer to attached continuation sheet.



ss References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs refer referenced in the current ication)

NDA
NDA 20-522 (Genentech, Inc.)
NDA 19-676 (Genentech, Inc.)
DMF
DMF
NDA 20-168 (Genentech, Inc.)
DMF
DMF
DMF
NDA 19-107 (Genentech, Inc.)
NDA 20-656 (Genentech, Inc.)

ADVISORY COMMITTEE MEETING

NOT NEEDED

APPEARS THIS WAY
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FEDERAL REGISTER NOTICES, OTC, OR DESI DOCUMENTS

NONE

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ADVERTISING MATERIAL

Requested in Action Letter

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