CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-075

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 21-075 for Nutropin Depot

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DMEDP/ODE II/ORM/CDER HFD-510

Letter Date: 25 June 1999
Stamp Date/Date Received, CDER:: 28 June 1999
Date Received, Medical Officer: 2 July 1999
Date Review Completed: 19 November 1999

Drug Name: Nutropin Depot
Generic Name: Somatropin (rDNA origin) for Injectable Suspension
Proposed Trade Name: Nutropin Depot
Previous Name During Drug Development: [redacted]
rhGH

Sponsor: Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990
Manufacturer: [redacted]

Table of Contents

1.1 Pharmacological Category: Recombinant human growth hormone (rhGH) (in new sustained-release formulation).

NDA Drug Classification:

Related Drugs: All of the rhGH products - all presently formulated for daily injection.

1.2 Indication: Long term treatment of patients with growth failure due to lack of endogenous GH secretion

1.3 Dosage Form, Dosage Recommended and Route of Administration: Reconstituted injectable suspension to be administered subcutaneously (SC). The proposed dosages are 1.5 mg/kg in one monthly injection or 0.75 mg/kg twice monthly.

1.4 On-Site Inspections by CDER: It was decided by this medical reviewer and his team leader than on-site inspections could be waived for this submission because of the small numbers of patients treated at any give site.

1.5 Correspondence with Sponsor/Genentech:

8/20/99 Dr. Malozowski (Team Leader) calls Ms. Fiona Cameron (Senior Manager, Regulatory Affairs), and requests Efficacy Update for Study 03-003.
8/31/99 Ms. Cameron faxes back proposed content of Efficacy Update and promises delivery of same on or about 9/20/99.
9/8/99 Telcon involving myself, Dr. Malozowski, and others at DMEDP/CDER, and Dr. Attie, Ms. Cameron, and others at Genentech and [redacted] Primary topic was disposition of patients in the different trials and planned content of Efficacy Update.
9/20/99 Efficacy Update arrives as planned.
10/8/99 Safety Update arrives as planned.
10/12/99 Telcon involving myself and Ms. Cameron, Dr. Attie and multiple others at Genentech and [redacted] Questions posed by me and answered, and new questions and requests generated during discussion, mostly regarding safety issues (i.e., injection site reactions and "post-dosing" headache and nausea). Genentech promises to reply by fax, hard copy and floppy disc.
10/20-21/99 Fax, hard copy and disc with tables and other data received by me as planned.
10/21/99 Telcon involving myself and Ms. Cameron. Content of 10/20/99 fax discussed, and new questions and requests posed by

me regarding safety issues noted above and injectate concentrations.
10/26/99 Fax with tables and other data received by me.
10/27/99 Telcon involving myself and Ms. Cameron regarding material received on 10/26/99. New requests for tables and data posed by me, mostly regarding injection site-related adverse events.
11/1/99 Fax and disc with information requested received by me.
11/1/99 Telcon involving myself and Ms. Cameron. New requests for tables and data posed by me regarding similar safety issues.
11/2/99 Fax and disc with information requested received by me.
11/2/99 Telcon involving myself and Ms. Cameron regarding material received on 11/2/99. New requests for tables and data posed by me regarding similar safety issues.
11/5/99 Disc with tables requested received by me.
11/15/99 Telcon involving myself and Ms. Cameron and 11/17/99 Telcon involving myself, Dr. Malozowski and Ms. Cameron. Both Telcons related to injection number information we would like to put in label. This remains an open item at the time this review is submitted. Genentech is trying to obtain information.

2.1 Materials Reviewed:

All clinical data in the original 6 volume submission. The data were primarily reviewed electronically after the NDA submission was placed on a secure website by CDER personnel.

Efficacy Update received on 9/20/99 and Safety Update received on 10/8/99 - also reviewed electronically.

Multiple faxes and 4 floppy discs noted in Section 2.1.

2.2 Relevant INDs and NDAs:

Nutropin	NDAs 19-676 and 20-168
Nutropin AQ	NDA 20-522
Protropin	NDA 19-107
[redacted] rhGH	IND [redacted]

3 Chemistry/Manufacturing Controls

See Chemistry Review and Formulation Section of [redacted]03-002 review. Nutropin Depot [somatropin (rDNA origin) for injectable suspension], referred to as [redacted] rhGH during development, is a sustained-release formulation of somatropin (rhGH, Genentech). Sustained release of rhGH is achieved utilizing the [redacted]

[redacted] In this system, following SC injection, rhGH is gradually released into the SC space from biodegradable, biocompatible microspheres containing micronized particles of rhGH (stabilized with zinc) embedded in a poly D/L lactide co-glycolide (PLG) co-polymer matrix. This polymer has been used safely in humans treated with the FDA-approved product, Lupron Depot (a sustained-release formulation of luteinizing hormone releasing hormone agonist [NDA 20-263]), as well as in suture material and bone plates.

4. Preclinical Pharmacology/Toxicology

See Pharmacology/Toxicology Review. In view of the well known properties of rhGH, a standard battery of toxicology studies was not required. The only remarkable finding in the studies that were performed was a significant number of local injection site reactions in juvenile monkeys.

5. Related Clinically Oriented Reviews

5.1 Statistical Review

See Statistical Review. The medical reviewer collaborated frequently with the statistical reviewer. Her insights and statistical expertise were invaluable to this reviewer.

5.2 Biopharmaceutics Review and Human Pharmacology, Pharmacokinetics (PK) and Pharmacodynamics (PD)

See Biopharmaceutics Review. The medical reviewer collaborated frequently with the biopharmaceutics reviewer. Comments regarding rhGH PK and PD (i.e., biologic markers of rhGH effect) can be found in clearly labeled sections within each study-specific review. Most significantly, the bioavailability of rhGH after a single injection of Nutropin Depot was ~33% of the bioavailability of rhGH provided by daily injections for a month. The is the most likely explanation for the relative lack of efficacy of Nutropin Depot in these clinical trials.

6 Clinical Background

6.1 Post-Marketing Experience None.

6.2 Foreign Experience None.

6.3 Relevant Literature

Literature regarding the use of rhGH in the treatment of children with growth hormone deficiency was reviewed for the last 15 years. Appropriate references are cited in the text of this review and a list of references appears at the very end of the review and in the appendix as well.

6.4 Relevant Background Information/Rationale for all Clinical Studies

The standard growth hormone (GH) treatment regimen for children with growth hormone deficiency (GHD) utilizing pituitary-derived non-recombinant GH which ended in 1985 involved a 3 times weekly (TIW) dosing schedule because it permitted rationing of scarce supplies of hormone, and was convenient and efficacious (Frasier, 1983). Less frequent administration of GH at similar doses resulted in lower growth velocities (Moore, 1987). After the introduction of recombinant human GH (rhGH) in 1985, the TIW schedule continued to be used routinely because of historical precedence and the results of clinical trials. Subsequently, the effects of daily vs. TIW administration of rhGH were compared in GH-deficient children. Early studies revealed an enhancement of growth velocity with daily rhGH administration mainly in the first year of treatment (Smith, 1988; Stubbe, 1992). In the most definitive randomized study to date, 0.3 mg/kg/week of rhGH was administered to 2 groups of naïve prepubertal GH-deficient children either daily or TIW (MacGillivray, 1996). During each of the 4 years, the children receiving daily injections of rhGH had a significantly greater annual growth velocity and, after 4 years of therapy, these children had grown 9.7 cm more than the children receiving TIW injections. Therefore, for the better part of the last decade, most GH-deficient children have been treated with daily (or 6 times/week) injections of rhGH. It should be further noted at this point that several studies earlier in this decade demonstrated that 0.3 mg/kg/week (43 ug/kg/day) (the amount of rhGH recommended by the Agency and used by MacGillivray et al in

the study described above) was the dosage of daily rhGH which resulted in optimal growth velocity (Anhalt, 1994 and De Muinck, 1994).

However, the inconvenience of a dosing regimen requiring daily injections remains a significant issue. This has resulted in varying degrees of noncompliance in as many as 50% of children treated with daily rhGH for GHD (Smith SL, 1993). In addition, 900 (~15%) of the 5,700 children in the National Cooperative Growth Study (NCGS) database who prematurely discontinued therapy with rhGH reported some problems with injections (Root, 1998). Hence, approximately 7.5% (900/12,000) of all patients in the NCGS database who initiated rhGH treatment may have discontinued therapy at some point for reasons related to injection aversion. Therefore, subjects who, for whatever reason, are unable or unwilling to take daily injections may be better served by a longer acting formulation.

Nutropin Depot [somatropin (rDNA origin) for injectable suspension], referred to as [redacted] rhGH during development, is a sustained-release formulation of somatropin (rhGH, Genentech). It was developed by [redacted] in partnership with Genentech, Inc., to provide a way to reduce the frequency of rhGH injections and increase the convenience of rhGH administration for pediatric patients with GHD (thereby hopefully increasing compliance as well). The depot formulation provides a sustained release of rhGH for up to 1 month and therefore requires only once- or twice-monthly dosings. The availability of Nutropin Depot provided the opportunity to evaluate the safety and efficacy of less frequent administration of rhGH, and to investigate the endocrine and metabolic effects of sustained delivery of rhGH, in children with GHD.

7 Description of Clinical Data Sources

7.1 Study Design for Clinical Trials [redacted]03-002, [redacted]03-004 and [redacted]04-003 - Including Rationale for Dosage Selection

Note: All doses of Nutropin Depot described from this point onward in this review refer to the amount of rhGH administered and do not reflect the weight of the injected microspheres. The first dose regimen of Nutropin Depot tested in humans was 0.75 mg/kg which was administered as a single SC injection to 13 adults with GHD in study [redacted]03-001. The 0.75 mg/kg dose was approximately equivalent to the maximum total monthly dose used

in studies in GHD adults at that time (25 ug/kg/day x 30 days) and represents about 60% of the total monthly dose currently recommended for children with GHD (43 ug/kg/day x 30 days). Levels of GH, insulin-like growth factor I (IGF-1) and IGF-binding protein 3 (IGFBP-3) increased from baseline and remained elevated for greater than 21 days. The injections were generally well tolerated. Minor injection site reactions and transient nausea and vomiting were noted in some subjects. Antibodies against GH were not detected in any of the subjects.

Based on the GH serum profile, IGF-I response, and tolerability data obtained from study [redacted]03-001, 0.75 mg/kg SC every 4 weeks (0.75q4) was chosen as the initial dose for pediatric subjects with GHD in study [redacted]03-002. [redacted]**03-002 was a 6 month, open label, Phase I/II, multicenter study** which evaluated the safety and efficacy of Nutropin Depot in naïve and previously treated prepubertal children with GHD. Subject eligibility criteria and trial endpoints were similar to those used in studies performed by Genentech to obtain approval of Nutropin and Nutropin AQ in this population (NDAs 19-676 and 20-522). The results of an interim 3 month analysis suggested that the 0.75q4 dose was safe and well tolerated, but based on the annualized growth rates, GH pharmacokinetic (PK) data and IGF-I levels, the dose could be increased. Therefore, 2 dose groups were added to study [redacted]03-002: 1.5 mg/kg SC every 4 weeks (1.5q4) and 0.75 mg/kg SC every 2 weeks (0.75q2) (a single adjusted dosage of not >1.5q4 had been projected in the original protocol).

The most frequent adverse events reported during study [redacted]03-002 were injection site reactions. Drug administration procedures were modified during subsequent studies in an attempt to improve the tolerability of Nutropin Depot injections. After 6 months of treatment, the mean 6 month annualized growth rate achieved in the 0.75q4 dose group was 7.6 cm/yr, whereas the growth rates achieved in the 1.5q4 and 0.75q2 dose groups were 8.3 cm/yr and 8.9 cm/yr, respectively. In addition, 2 patients with hypoglycemia as a manifestation of GHD prior to therapy reported continued hypoglycemic events while being treated with 0.75q4. Therefore, the 1.5 mg/kg 1x/month (1.5 1x/mo) and 0.75 2x/mo dosing regimens were chosen for the Phase III study, [redacted]03-004.

[redacted]**03-004 was a 6 month, open label, randomized, pivotal, Phase III, multicenter study** which evaluated the safety and efficacy of Nutropin Depot in naive prepubertal children with GHD. Subject eligibility criteria, efficacy endpoints and safety parameters were similar to those used in [redacted]03-002 (excepting the exclusion of children previously treated with rhGH).

Subjects completing the 6 month "feeder" studies 03-002 and 03-004 were eligible to continue in the **long term extension study, 03-003**. As in the case of study 03-004, for the reasons already stated above, the 1.5 1x/mo and 0.75 2x/mo dosing regimens were chosen for the extension study, 03-003. Patients treated with 0.75q4 during study 03-002 who chose to enter study 03-003 were randomized to receive either 1.5 1x/mo or 0.75 2x/mo. Efficacy endpoints and safety parameters were similar to those used in the "feeder" studies (excepting the measurement of annual as opposed to annualized growth rates).

Table 1. Brief Summary of Clinical Trials*

Study Number	# of Sites	Design	Treatment Arms (n)	Duration of Treatment	Patient Type
03-002	12	Open Label, Phase I/II	0.75q4 (19) 0.75q2 (20) 1.5q4 (25) Total n=64	6 months	Naïve and Currently Treated patients
03-004	27	Open Label, Randomized, Phase III	0.75 2x/mo (38) 1.5 1x/mo (36) Total n=74	6 months	Naïve patients only
03-003	12	Open Label, Extension Study Fed By 002 And 004	0.75 2x/mo (51) 1.5 1x/mo (45) 0.75q4 transiently Total n=96	12+ months	Naïve and Currently Treated patients

*Compiled by statistical reviewer

7.2 Patient Disposition See Tables 3 and 4 (03-002); Tables 12 and 13 (03-004); Tables 23 and 24 (03-003); Table 34** (ISS/ISE Overview)

7.3 Patient Demographics See Table 5 (03-002); Table 14 (03-004); Table 25 (03-003); Tables 36 and 39 (ISE)

7.4 Extent of Exposure Page 32 (03-002); Page 59 (03-004); Page 90 (03-003); Page 118 (ISS)

8 Reviewer's Critical Analysis of Individual Studies

8.1 [redacted]03-002

8.1.1.1 Objectives

The objective of this study was to demonstrate the safety and efficacy of a new sustained-release formulation of rhGH, Nutropin Depot, in the treatment of growth failure in children with GHD, and to determine the optimal dosages to utilize in the pivotal Phase III study.

8.1.1.2 Study Design/Description of Study

[redacted]03-002 was a Phase I/II, multicenter, open label, 6 month study which evaluated the safety and efficacy of a new sustained-release formulation of rhGH, Nutropin Depot, in naïve and currently treated (CT) prepubertal children with GHD. Thirty-eight subjects with GHD and CT with daily injections of rhGH, and 26 subjects with GHD and naive to rhGH treatment, were enrolled at 12 medical centers in the United States. Nutropin Depot was not administered to CT patients until 7 days after discontinuation of daily rhGH injections (washout period).

The first 6 subjects enrolled were CT with daily rhGH injections and were assigned to receive 0.75q4 of Nutropin Depot. As stated earlier, this dose represents ~60% of the total monthly dose currently recommended for children with GHD (0.043 mg/kg/day x 30 days). After satisfactory adverse experience profiles were obtained in these CT patients following 2 treatments, 6 naive subjects were subsequently treated with the same dose. The results of an interim 3 month analysis in these 12 patients suggested that the 0.75q4 dose was safe and well tolerated, but based on the annualized growth rates, GH PK data and IGF-I levels, the dose could be increased in an attempt to increase efficacy. Therefore, 2 higher dose groups were added (1.5q4 and 0.75q2) and additional subjects were recruited and assigned as follows: 4 more CT (total of 10) and 3 more naïve (total of 9) subjects received 0.75q4, 17 CT and 8 naive subjects received 1.5q4, and 11 CT and 9 naive subjects received 0.75q2 (a single adjusted dosage of not >1.5q4 had been projected in the original protocol)

The PK profile of GH released from Nutropin Depot and serial IGF-I levels were determined in all subjects to varying degrees. The majority of patients were sampled periodically and a subset of subjects receiving 0.75q4 and 1.5q4 underwent intensive sampling to determine GH PK parameters and IGF-I levels.

8.1.1.3 Protocol

Protocol Amendments

The protocol was amended 6 times. The following are the most significant changes made: 1) The second amendment, dated 4 December 1996 (Serial No. 007 to IND [redacted], changed the Nutropin Depot diluent from a solution of [redacted] to one of carboxymethylcellulose (CMC), increased the diluent volume from [redacted] mL to 1.5 mL, and revised the study drug preparation and administration procedures - this amendment was essential because the original diluent resulted in needle clogging and failed injections; 2) The fourth amendment, dated 4 March 1997 (Serial No. 011 to IND [redacted], added a third dose group of 12 CT and 8 naive subjects who received 0.75q2.

Materials and Methods

Subjects

Subject Selection

Sixty-four GHD children, 38 of whom were CT with daily rhGH injections and 26 of whom were naive to rhGH treatment, were enrolled in the study and assigned to receive 1 of the following 3 dose regimens of Nutropin Depot:

Group 1: 0.75q4 (10 CT and 9 naive subjects)
Group 2: 1.5q4 (17 CT and 8 naive subjects)
Group 3: 0.75q2 (11 CT and 9 naive subjects)

Inclusion Criteria

Subjects had to fulfill the following criteria to be eligible for entry into the study:

---Documented GHD in both naive and CT subjects by a maximum GH response of <10 ng/ml on at least 2 prior standard pharmacologic

tests of GH secretory capacity (insulin-induced hypoglycemia, arginine, clonidine, or L-dopa)

---Bone age of <9 years for girls and <10 years for boys

---Prepubertal Tanner Stage 1 for breasts (girls) or genitalia (boys)

---Subjects with multiple hormone deficiencies stabilized on L-thyroxine or hydrocortisone for at least 6 months prior to enrollment

---For naive subjects, height that was >2 standard deviations (SD) below the normal mean for their age and sex

---For CT subjects, on continuous rhGH therapy for at least 1 year prior to study entry **at an average dose of 0.25–0.35 mg/kg/week administered 6 or 7 times/week** (there was a 7 day washout period for daily rhGH prior to dosing with Nutropin Depot)

---Height data available for at least 6 months prior to the study for CT subjects

---Willingness and ability to participate in study assessments

---Consent form signed by parent or legal guardian

Reviewer comment:

The fact that subnormal height velocity was not used as an inclusion criteria brings up the possibility that children who were not truly GH deficient were enrolled. It is well established that GH provocative testing does not necessarily predict the response to exogenous rhGH therapy (Vance, 1999). However, when used in conjunction with *growth velocity <25th percentile (as well as standardized height <-2 to -2.5 and very delayed bone age), a peak serum GH response <10ng/ml in response to stimulation is a reasonable definition of GHD (with values <5 ng/ml reflecting the most severe deficiency) (Vance, 1999). If patients who were not as potentially responsive to exogenous rhGH therapy were enrolled, this would diminish the efficacy seen in this study.

Exclusion Criteria

Subjects who met any of the following criteria were excluded from study entry:

---Diabetes mellitus

---Treatment with anabolic agents

---Current treatment with methylphenidate or cyproheptadine

---Growth failure due to other reasons including acute or chronic genitourinary, cardiopulmonary, gastrointestinal, or nervous system disease, and nutritional/vitamin deficiency
---Growth failure due to chromosomal abnormality or osteochondrodystrophy
---Hypothalamic/pituitary tumors diagnosed or treated in the past year
---Allergy or sensitivity to any components of Nutropin Depot formulation
---Known bleeding disorders

Reviewer comment:

Method of Treatment Assignment

This was an open-label study. Subjects were recruited by the participating investigators from their patient population. The first subjects recruited by the investigators were CT with daily injections of rhGH and were assigned to receive 0.75q4. After review of the safety data, subjects who were naive to treatment were recruited and assigned to the same dose. After the 3 month interim analysis suggested the need for higher dose groups, the same method was followed with the 1.5q4 and 0.75q2 dose groups, with CT subjects enrolled first. As subsequent subjects were identified, they were assigned to an open dose group.

Study Treatment

Formulation

Nutropin Depot [somatropin (rDNA origin) for injectable suspension], referred to as rhGH during development, is a sustained-release formulation of somatropin (rhGH, Genentech). Sustained release of rhGH is achieved utilizing the In this system, following SC injection, rhGH is gradually released into the SC space from biodegradable, biocompatible microspheres containing micronized particles of rhGH embedded in a PLG co-polymer matrix.

The Nutropin Depot diluent used initially was [redacted] for injection. When the first 6 patients in this study were treated, multiple injection failures resulted because of needle clogging. To prevent clogging, several steps were instituted: the diluent was changed to a CMC solution (CMC sodium salt, polysorbate 20, sodium chloride, and water for injection), the volume of the diluent was increased from [redacted] mL to 1.5 or [redacted] mL, and a larger (22 gauge) needle was used. Additionally, at each study site, individual training was given on resuspension and injection techniques to the health care professional responsible for administering the injections.

Nutropin Depot is stored at 2-8° centigrade and Nutropin Depot diluent is stored at room temperature.

Dosage and Administration

The dose for each subject was calculated according to the individual's weight at each visit and was administered as a SC injection. Subjects received 0.75 mg/kg of Nutropin Depot once or twice monthy or 1.5 mg/kg of Nutropin Depot monthly. Nutropin Depot was carefully suspended in 1.5 ml or 1 ml of the Nutropin Depot CMC solution diluent. The deliverable rhGH in each vial was 22.5 mg at all times and the rhGH concentration was 16 mg/ml or 22 mg/ml (i.e., concentration was determined by overaged amount of rhGH added to the vial ÷ diluent added + volume displaced by the microspheres). Care was taken to produce a uniform homogeneous suspension of microspheres which was injected immediately from a 3 ml syringe with a 1 inch, 22 or 23 gauge needle. Administration of all doses of Nutropin Depot in this particular study was done by a trained health care professional.

****If the total volume for any dose exceeded 1 mL, the dose was divided into 2 or more injections of equal volume.**

Dosage Modification

The dose level of Nutropin Depot for each subject remained the same throughout the study.

Concomitant Therapy

Subjects with adrenocorticotrophic hormone (ACTH) deficiency could have received hydrocortisone at a dose that did not interfere with growth (physiologic replacement dose) and subjects with hypothyroidism could have received L-thyroxine. Dosage of either medication must have been stable for 6 months prior to the study. Other medications that were considered necessary for the subject's welfare and for which there was no evidence they could interfere with the study medication or affect growth were given at the discretion of the investigator.

8.1.1.4 Study Assessments

Screening and Pre-treatment Assessments

To confirm subject eligibility and to establish baseline measurements, the following assessments were made within 2 weeks of the first dose of Nutropin Depot:

---Verification that all admission criteria were met, including documentation of GHD based on at least two GH stimulation tests
---Medical history, including prior height data
---Complete physical examination, including height, weight, and Tanner stage
---Bone age X-ray (within 3 months, prior to first dose)
---Complete blood count (CBC) with differential and platelet count
---Complete urinalysis (UA) with microscopic examination
---Serum chemistry panel, including total protein, albumin, globulin, A/G ratio, total bilirubin, ALT (SGPT), AST (SGOT), alkaline phosphatase, GGT, LDH, BUN, creatinine, uric acid, calcium, inorganic phosphorous, cholesterol, sodium, potassium, chloride, CO2
---T3 and Free T4
---Hemoglobin A1C
---2 hour glucose tolerance test (fasting and 2 hour glucose and insulin levels)
---Anti-GH antibodies
---GH, IGF-I, GH binding protein (GHBP), IGFBP-3

Assessments during Treatment

Efficacy Parameters

The primary efficacy endpoint was the 6 month annualized growth rate. The 3 month annualized growth rate was determined as well.

Secondary efficacy endpoints included height age, standardized height [height standard deviation score (SDS)], and bone age. The titer and binding capacity of anti-GH antibodies were determined as well.

The 6 month annualized growth rate was computed as follows: Height at 6 Month Visit - Baseline Height ÷ Date at 6 Month Visit - Baseline Date multiplied by 365 days

The pre-study growth rate was determined as follows: For CT subjects, several height measurements at least 6 months prior to the start of the study were prospectively collected. The height used for the pre-study growth rate had to be at least 6 months prior to study start and no more than 425 days (i.e., ~1 year and 2 months) prior to study start. For naive subjects, several height measurements at least 6 months prior to the start of the study were retrospectively collected. The height used for the pre-study growth rate was that obtained at least 153 days prior to study start and no more than 425 days (i.e., ~1 year and 2 months) prior to study start. Any pre-study growth rates based on heights outside of these boundaries were considered unreliable estimates of pre-study growth rate and were not used.

All heights reported during the study were an average of 3 heights with the exception of the baseline pre-study height for which only 1 height measurement was required. The means and standard deviations of height for age and sex for normal subjects were derived from the percentiles published by the National Center for Health Statistics (Hamil, 1979). The height age of a subject is equal to the age at which the mean height of normal children of the same sex is equal to the subject's height.

Standardized Height/Height SDS was computed as follows: Actual Height - Mean Height of Normal Subjects of Same Age and Sex/Height SD of Normal Subjects of Same Age and Sex. Height standardized for age and sex permits comparisons of subjects'

heights with normal children of the same chronological age and sex.

Bone age determinations using the Fels method were performed at the Fels Institute (Yellow Springs, OH) by a reviewer masked to information relative to subject and dose (Roche, 1988). Anti-GH antibody titer and binding capacity determinations were performed by Genentech, Inc. (South San Francisco, CA).

Height, weight and Tanner stage were determined monthly during the study, bone age was reassessed after 6 months of Nutropin Depot therapy, and anti-GH antibody measurements were performed after 3 and 6 months of Nutropin Depot therapy.

Safety Parameters

Safety assessments were made based on adverse event reports, and monthly physical examinations and laboratory studies (exceptions: glucose tolerance testing (GTT) was reassessed after 3 and 6 months of therapy and thyroid function was reassessed after 6 months of therapy). See Table 2 below.

Table 2. [redacted]03-002 - Flowchart of Baseline and On-Study Efficacy and Safety Parameters

Evaluations	Baseline	24 hours post-dose	Monthly	@ end of month 3 only	@ end of month 6 only
Assessment of injection site reaction	X		X		
Medical history	X				
Interval medical history			X		
Physical exam	X		X		
Height	X		X		
Weight	X		X		
Tanner stage	X		X		
Bone age	X				X
Anti-GH antibodies	X			X	X
CBC, diff, platelets	X	X	X		
Complete UA	X		X		
Chemistry panel	X	X	X		
T3, Free T4	X				X
Hemoglobin A1C	X		X		
2 hour GTT with glucose & insulin levels	X			X	X

PK Parameters and Biologic Markers (with both safety and efficacy implications)

The PK profile of GH released from Nutropin Depot and IGF-I levels were investigated in all subjects to varying degrees. In the majority of subjects, GH and IGF-I levels (as well as IGFBP-3 and GHBP) were obtained at baseline, pre-dose, 24 hours post-dose (peak level), on Days 7 and 14 (trough level for 0.75q2 dose group), as well as on Days 21 and 28 (trough level) in the 0.75q4 and 1.5q4 dose groups. In addition, a subset of patients receiving 0.75q4 and 1.5q4 underwent intensive sampling for GH and IGF-I levels. Serum levels of GH, IGF-I, IGFBP-3, and GHBP obtained during the initial-release (0-2 days) and subsequent sustained-release phases (2-14 or 2-28 days) were compared with those obtained during the baseline period and with desired levels.

Determination of GH, IGF-I, IGFBP-3 and GHBP levels was performed by [redacted]

Subject Discontinuation

Subjects were discontinued for the following reasons:
---Medical conditions that required study discontinuation
---Intercurrent illness that could have, in the judgment of the investigator, tended to affect assessments of clinical and mental status to a significant degree
---Noncompliance with the protocol
---Subject, parent, or guardian desire to discontinue participation

Subject Replacement

Subjects who discontinued prior to completing the third treatment cycle were replaced in the same dose group.

8.1.1.5 Statistical Analysis

Efficacy Analysis

Naïve patients: The planned primary analysis of growth rate was to perform an analysis of covariance (ANCOVA) (using age as a covariate), wherein the 6 month annualized growth rate of naive subjects in the different dose groups would be compared with the

annual growth rate of age-matched controls treated with daily rhGH in Genentech study L0368g (NDA 20-522, Nutropin AQ). With 21 naive patients, the trial was powered to detect a 2.7 cm/yr difference in growth rate between the 6 month annualized growth rate of the naïve subjects in this study and the annual growth rate of the subjects from study L0368g. Instead, because of the small sample sizes in each dose group, the 6 month annualized growth rate estimates along with the corresponding confidence intervals (CI) are presented for each dose group.

CT patients: For CT patients, a paired t-test was proposed in the protocol to compare the annualized growth rate of patients receiving daily injections of rhGH prior to entry into the study with the 6 month annualized growth rate of these same patients after 6 months of Nutropin Depot therapy. With 10 CT patients, the trial was powered to detect a 2.2 cm/yr difference in the annualized growth rates prior to the study and after 6 months of Nutropin Depot therapy.

Reviewer Comment:
As pointed out by the statistical reviewer, no criteria for efficacy were defined in the protocol. It is not clear whether Nutropin Depot was expected to be comparable to or better than the historical comparator (daily injections). No measure of comparability is mentioned in the protocol. The power calculations suggest that a difference of 2.7 cm/yr in the first year of therapy of naïve patients would be considered clinically important (i.e., if the Nutropin Depot resulted in a growth rate within 2.7 cm (~1 SD) of that achieved with daily injections, it would be considered efficacious) and that a difference of 2.2 cm/yr (~1 SD) during the maintenance therapy of CT patients would be considered clinically important (i.e., if the Nutropin Depot resulted in a growth rate within 2.2 cm of that achieved with daily injections, it would be considered efficacious).

Summary statistics for height, standardized height, and height age are presented at pre-study and Month 3 for subjects who completed 3 months, and at pre-study and Months 3 and 6 for subjects who completed the study. These were done by dose group and subject group. Summary statistics for bone age are presented at pre-study and Month 6 for subjects who completed the study. In addition, the change in bone age minus the change in height age at Month 6 is presented. Although the results indicated that Nutropin Depot was efficacious, the usefulness of these parameters over a 6 month period are limited and the sponsor chose not to discuss these findings in the submission.

The percentage of subjects with positive anti-GH antibody results and the antibody titer levels were summarized at baseline and at Months 3 and 6 for each a titer of >1.0 were assayed for binding capacity dose group, CT, naive, and all subjects. All samples with and the results summarized.

Safety Analysis

Adverse events are tabulated by COSTART preferred term and body system for each dose group for CT, naive, and all subjects. Injection site adverse events are tabulated separately from non-injection site events. The number of injection site events is also presented for each dose group for CT, naive, and all subjects.
Laboratory and other safety values (including vital signs) are summarized with simple descriptive statistics, including means and SD at baseline, 24 hours post-dose, and at the end of Months 3 and 6, by subject group and by dose group.

Data Quality Assurance

Accurate, consistent, and reliable data were ensured through the use of standard practices and procedures.
Given the paucity of patients at each testing site, it was not felt that on-site inspections by the Agency were necessary.

8.1.2 Results

Subject Eligibility and Treatment Assignment

Sixty-four prepubertal subjects with GHD were enrolled at 12 medical centers in the United States. Thirty-eight subjects were currently being treated with daily rhGH for an average of 2.9 years (range, [redacted] years), and 26 subjects were rhGH naive. Subjects were assigned to receive one of the following regimens of Nutropin Depot:

----Group 1: 0.75q4 (10 CT and 9 naive subjects)

----Group 2: 1.5q4 (17 CT and 8 naive subjects)

----Group 3: 0.75q2 (11 CT and 9 naive subjects)

Protocol Violations and Deviations

Five patients were allowed into the study with only 1 (rather than 2) abnormal GH stimulation tests. Two patients had a bone age >10 at study entry - 1 of them had received twice the dose of daily rhGH delineated in the inclusion criteria as part of another clinical trial. Other protocol deviations and violations were inconsequential.

8.1.2.1 Patient Disposition

Table 3 depicts the number of patients assigned to the 3 dosage levels for CT and naïve patients. Nineteen patients were assigned to 0.75q4, 25 to 1.5q4, and 20 to 0.75q2.

The 19 patients dosed with once a month doses of 0.75 mg/kg (both naïve and CT patients) were entered into the trial during the first 4 months at 7 sites. As stated earlier in this review, based on an interim 3 month analysis of efficacy and safety, all subsequent patients entering the trial were placed on the 2 larger doses. More CT patients (38) were treated in this study than naïve patients (26).

Enrollment at all 12 sites was not begun at the same time. The first 6 patients were enrolled at 2 sites during the first month. An additional 9 sites enrolled patients for the next 8 months, and one site enrolled only CT patients after enrollment was complete at the other 11 sites.

Table 3. [redacted]03-002 - Patient Disposition*

	0.75 mg/kg once a mo		0.75 mg/kg twice a mo		1.5 mg/kg once a mo	
	CT	Naïve	CT	Naïve	CT	Naive
Entered (n=64)	10	9	11	9	17	8
Completed 3 mos (n=59)	9	9	11	9	13	8
Completed 6 mos (n=52)	6	7	11	9	12	7
Completed 6 mos and had pre-study growth rate (n=45)	6	3	11	8	12	5
Continued into [redacted]03-003 (n=35)	5	5	4	9	6	6

*Table compiled by statistical reviewer

Dropout rates related to adverse events were similar in CT patients (4/38, 11%) and naïve patients (3/26, 12%). No dropouts for any reason occurred in the 0.75q2 dose group and dropout rates related to adverse events were similar in the

0.75q4 (4/19, 21%) and 1.5q4 (3/25, 12%) dose groups. The most common adverse event leading to dropout was injection site pain in both CT and naïve patients. See Table 4 below.

Table 4. [redacted]03-002 - Reasons for Discontinuation*

	0.75 mg/kg once a mo		0.75 mg/kg twice a mo		1.5 mg/kg once a mo	
	CT	Naïve	CT	Naïve	CT	Naive
Entered (n=64)	10	9	11	9	17	8
Discontinued (n=12)	4	2	0	0	5	1
Reasons for discontinuation						
Adverse event (n=7)	2	2	0	0	2	1
-Hypoglycemia (n=2)	2	0	0	0	0	0
-Injection site pain (n=4)	0	2	0	0	2	0
-Allergic reaction (n=1)	0	0	0	0	0	1
Subject request (n=4) (no reason given)	1	0	0	0	3	0
Other (n=1)	1	0	0	0	0	0

*Table compiled by statistical reviewer

8.1.2.2 Patient Characteristics

Most of the patients were male and Caucasian. More than 90% had idiopathic GHD; none of the naïve patients and only 4/38 CT patients had an organic etiology. Chronological age ranged from 3 to 14. The mean chronological age/bone age for CT patients was 9.6/8.2 years; the mean chronological age/bone age for naive patients was 7.7/5.6. Utilizing the criteria stated earlier in this review, all CT patients and 18/26 naïve patients had acceptable pre-study growth rates. The average pre-study growth rate was 8.2 cm/yr (range, [redacted] cm/yr) in CT patients and 5.6* cm/yr (range [redacted] cm/yr) in naïve patients. Mean standardized height was -1.3 in CT patients and -3.1 in naïve patients. See Table 5 below.

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Table 5. [redacted]03-002 - Patient Characteristics*

Characteristic	All dose groups		0.75q4		0.75q2		1.5q4	
CT=38 Naïve=26	CT	Naïve	CT	Naïve	CT	Naïve	CT	Naive
Male (%)	66%	73%	80%	78%	55%	78%	65%	63%
Etiology (%)								
Idiopathic	89%	100%	90%	100%	82%	100%	94%	100%
Organic	11%	0%	10%	0%	18%	0%	6%	0%
Age (years)	9.6	7.7	9.3	9.3	9.4	7.4	9.9	6.3
Range	4-14	3-14	6-11	3-14	4-13	6-11	7-14	4-11
Bone Age (years)	8.2 n=35	5.6 n=25	8.1	6.9	7.9	5.5	8.5	4.0
Previous Growth Rate (cm/yr)	8.2	5.5*	8.3	5.2	8.6	5.6*	7.9	5.6*
Range	[redacted]							
Race (%)								
White	91%	89%	90%	89%	100%	78%	82%	100%
Weight (kg)	29	19						
Height (cm)	128	108	131	117	126	105	128	101
Standardized Height	-1.3	-3.1	-0.6	-2.75	-1.5	-3.5	-1.5	-3.0

*Table compiled by statistical reviewer

Reviewer Comment:

Regarding naïve patients: It is noteworthy that the mean pre-study growth rate was relatively robust in the naïve cohort (5.6 cm/yr with range, [redacted] cm/yr). Typical patients with GHD usually have growth rates <25th percentile compared with age- and sex-matched normals (using percentiles published by the National Center for Health Statistics 7.7 year old GHD males [the mean age of the mostly male naïve patients in this study] should have a mean growth rate <4.8 cm/yr*), and more often than not less than 5 cm/yr. In a landmark study published by MacGillivray et al, comparing the efficacy of daily versus TIW rhGH in naïve patients, the baseline growth rate was 4.2 cm/yr (range, 1 to 6 cm/yr; mean age 8.2; n=50). This observation relates directly to the comment I made earlier in this review about diminished growth velocity NOT being an inclusion criteria for this trial! I am now even more concerned that some patients who were not truly growth hormone deficient were included in the treatment arms. This could help explain the lesser efficacy of Nutropin Depot compared with daily rhGH which will be discussed further ahead in this review. *Caveat: One must be cautious superimposing the growth rates of children with GHD (baseline and indeed after rhGH therapy) on a normative curve of growth velocities.

Regarding CT patients: As pointed out by the Agency's statistical reviewer, a record of rhGH treatment compliance prior to entering the trial was not available. The estimates of pre-study growth rates may therefore be biased by patient selection. More precisely, patients less compliant on daily therapy with rhGH may be more likely candidates for this trial, and their pre-study growth rates may be less than what is normally observed for patients on daily therapy. Since it is well known that more severely GH deficient patients respond more robustly to rhGH therapy, these non-compliant patients (more lacking in GH due to the noncompliance) may therefore tend to respond more vigorously after the institution of totally compliant health care provider-administered Nutropin Depot therapy.

Compliance

Compliance with study procedures and visits was assessed to be adequate. Minor variations in some dose volume calculations were noted which were not felt to be significant.

Concomitant Therapy

The use of concomitant medications by subjects during the study was reviewed by the Medical Monitor. Ten subjects were treated with appropriate amounts of L-thyroxine replacement therapy for central hypothyroidism and 6 patients (all of whom were hypothyroid as well) were treated with appropriate replacement doses of hydrocortisone for central hypoadrenalism. One patient was treated with desmopressin for diabetes insipidus. Other medications used by subjects were generally those prescribed to treat pre-existing conditions or routine childhood ailments.

8.1.2.3 Efficacy Results

Primary Efficacy Endpoint: 6 Month Annualized Growth Rate

The mean annualized growth rates of patients completing 6 months of therapy with Nutropin Depot and all treated patients (intent to treat [ITT] analysis with the last observed growth rate carried forward) are shown in Table 6 for each dose group in both naïve and CT subjects. Not surprisingly, the growth rates of naïve patients are clearly larger than the growth rates observed in the CT patients at all dose levels. There are no important differences between the 3 dose groups in naïve

patients as well as in CT patients - including the 0.75q4 dose which was eliminated from subsequent studies after a 3 month efficacy/safety interim analysis. The administration of 1.5 mg/kg of Nutropin Depot (the dose utilized by the sponsor in [redacted]03-004 and [redacted]03-003), either as a monthly injection or divided in half every 2 weeks, produces an equivalent result in naïve and CT subjects.

Table 6. [redacted]03-002 - 6 Month Annualized Growth Rates*

	0.75 mg/kg once a month		0.75 mg/kg twice a month		1.5 mg/kg once a month	
	CT	Naïve	CT	Naïve	CT	Naive
Pts with 6 mo data						
N	6	7	11	9	12	8
Mean cm/yr(SD)	5.2(3.7)	7.6(2.3)	5.2(1.3)	8.9(3.2)	5.0(2.5)	8.3(2.6)
95% CI	(1.7,8.7)	(5.5,9.7)	(4.2,6.0)	(6.5,11.3)	(3.4,6.6)	(6.2,10.4)
All Pts (ITT)						
- N	10	9	11	9	15	8
Mean cm/yr(SD)	5.1(3.0)	8.0(2.1)	5.2(1.3)	*8.9(3.2)	4.8(2.6)	*8.3(2.6)
95% CI	(3.0,7.2)	(6.3,9.6)	(4.2,6.0)	(6.5,11.3)	(3.4,6.2)	(6.2,10.4)

*Table compiled by statistical reviewer

Six Month Annualized Growth Rate in Naïve Patients:
According to the protocol, the sponsor planned to compare the annualized growth rates achieved in naïve patients after 6 months of Nutropin Depot therapy with a historical control, the annual growth rates of age-matched naïve patients treated with daily injections of rhGH in Genentech study L0368g (NDA 20-522, Nutropin AQ). The sponsor did not perform this comparison because of the small sample sizes in each treatment group - the trial was powered based on 21 naïve patients and only 17 naïve patients were given the amount proposed for marketing. The sponsor did provide summary data for the L0368g study. In Table 7 below, data for the naïve patients dosed with 0.75q2 combined with data for the naïve patients treated with 1.5q4 are compared with data from the L0368g study. As in the case of the mean annual growth rate of children treated with daily injections of rhGH in the L0368g study, the mean 6 month annualized growth rate achieved in the patients treated with Nutropin Depot was significantly greater than the pre-study mean annualized growth rate (delta=3.3 cm/yr, p=0.002, Wilcoxon signed rank test). (Note: A subset analysis comparing the mean on-study growth rate

of patients with pre-study growth rates <5 cm/yr with the mean on-study growth rate of patients with pre-study growth rates >5 cm/yr did not reveal meaningful information because of the small sample size and arbitrary cutpoint.) However, the mean annualized growth rate was significantly larger in the patients who received daily injections of rhGH compared with the group receiving Nutropin Depot (delta=2.3 cm/yr, p=0.005, t-test).

Table 7. [redacted]03-002 - Comparison of Mean Annualized Growth Rate in Naïve Patients Receiving 1.5 mg/kg/month of Nutropin Depot in Single or Twice Monthly Injections with Mean Annual Growth Rate in Naïve Patients Receiving Daily Injections of rhGH*

	N	Age	Bone age	Pre-study growth rate	Dose (mg/kg/mo)	Annualized Growth Rate
[redacted]03-002 (SD)	17	6.9 (2.4)	4.8 (2.3) n=13	5.4** (2.6)	1.5	8.7 (2.9)
L0368g (SD)	62	8.0 (3.4)	6.5 (3.1)	4.8 (2.3)	-1.33	11.0 (2.9)

*Table compiled by statistical reviewer
**Reflects data for 4 patients excluded by sponsor

Reviewer Comment:
Although [redacted]03-002 was not a prospective, randomized, actively controlled trial comparing Nutropin Depot with daily injections of rhGH in naïve patients, the use of the L0368g study as a historical control is reasonable in this instance because of the comparable demographics/baseline characteristics of the children in both trials with the exception of pre-study growth rate (i.e., chronological age, bone age, and the total amount of rhGH administered each month). (In addition, the same rhGH preparation [Nutropin, Genentech] was used in both studies.) Interestingly, MacGillivray et al found a similar highly significant difference (delta=2.6 cm) in first year mean annual growth rate when an identical amount of rhGH (0.3 mg/kg/week) was administered daily and compared with the same amount of rhGH administered less frequently, TIW. Moreover, review of the literature confirms the validity of the first year annual growth rate reported in the L0368g study (i.e., the administration of daily injections of rhGH [at the recommended dosage of 0.3 mg/kg/week or ~1.3 mg/kg/month] results in a first year growth rate of 10.7 to 11.9 cm [MacGillivray, 1996, n=28, first year mean annual growth rate=11.4 cm; Sponsor derived cohort from NCGS database in ISE for NDA 21-075 for Nutropin Depot and Root, 1999, n=1909, first year annualized growth rate=10.7 cm; Study

85-041, Nutropin, NDA 19-676, n=44, first year annualized growth rate=11.9 cm). Reviewer comments regarding possible explanations for the decreased efficacy observed in naïve subjects treated with Nutropin Depot compared with naïve subjects treated with daily injections of rhGH can be found further ahead in this review in the Efficacy Discussion section.

6 Month Annualized Growth Rate in CT Patients: According to the protocol, the on-study 6 month annualized growth rates (following 6 months of treatment with Nutropin Depot) were to be compared with pre-study annualized growth rates (following 6 months of treatment with daily injections of rhGH) using a paired analysis - but these results are not presented in the NDA. Figure 1 shows that only 4 patients achieved an improved growth rate when on-study growth rates are plotted against pre-study growth rates for individual patients in the CT cohort. Moreover, only 1/3 of the CT patients had an on-study annualized growth rate within 2.2 cm/yr of their pre-study annualized growth rate (the study was powered to detect a 2.2 cm/yr difference in the on-study and pre-study annualized growth rates). Both of these observations suggest that Nutropin Depot was less efficacious than daily injections of rhGH in the CT subjects.

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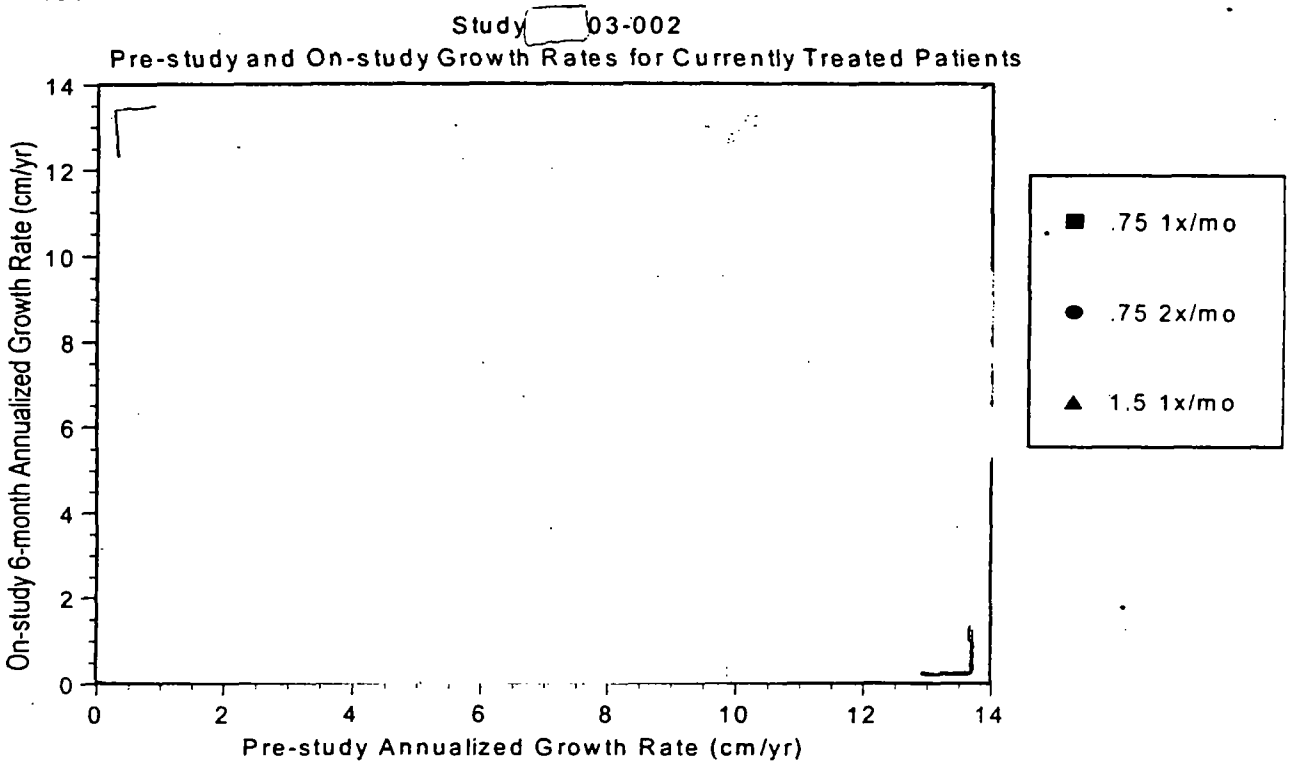
Figure 1. [redacted]03-002 - On-Study vs. Pre-Study Annualized Growth Rates in CT Patients



The mean annualized growth rates of CT patients completing 6 months of therapy with Nutropin Depot and all CT patients (ITT analysis) are shown in Table 8 for all 3 treatment groups and for the 2 larger dosages combined (i.e., 1.5q4 and 0.75q2). The mean annualized pre-study growth rates exceeded the mean annualized on-study growth rates by 3.1 cm/yr (ITT sample). In the ITT sample, paired differences for all treatment groups are either highly statistically significant or borderline significant ($p<0.06$ or <0.08).

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Table 8. [redacted]03-002 - Pre-study and On-study Mean Annualized Growth Rates for Currently Treated Patients*

	0.75q4	0.75q2	1.5q4	0.75q2 + 1.5q4 combined
Pts with 6 month data				
N	6	11	12	23
Pre-study rate	7.7(2.5)	8.6(2.2)	7.4(3.4)	8.0(2.9)
On-study rate	5.2(3.7)	5.2(1.3)	5.0(2.5)	5.0(2.0)
Paired difference**	-2.5(5.8)	-3.4(1.9)	-2.4(5.2)	-2.9(3.9)
Paired test p-value***	.31	.001	.15	.002
All Pts(ITT)				
N	10	11	15	26
Pre-study rate	8.3(2.9)	8.6(2.2)	7.9(3.4)	8.2(2.9)
On-study rate	5.1(3.0)	5.2(1.3)	4.8(2.6)	5.0(2.1)
Paired difference	-3.2(4.5)	-3.4(1.9)	-2.9(5.1)	-3.1(4.0)
Paired test p-value	.06	.001	.05	.0003

* Table compiled by statistical reviewer
** On-study rate minus pre-study rate
*** Results for Wilcoxon signed rank test for paired difference

Secondary Efficacy Endpoints

Standardized Height/Height SDS

In naïve subjects, mean pre-study height SDS ranged from -2.8 to -3.5 in the 3 dose groups. In naïve subjects with 6 month height data available, the mean height SDS increased by 0.3±0.2 in the 1.5q4 dose group and 0.4±0.3 in the 0.75q2 dose group. In CT subjects, mean pre-study height SDS ranged from -1.3 to -1.5 in the 2 higher dose groups. In CT subjects with 6 month height data available, mean height SDS did not change.

Bone Age

In naïve subjects, bone age at baseline was markedly delayed by an average of ~2.0 years relative to chronological age in all dose groups. The mean change in bone age after 6 months of treatment was 0.6 in the 1.5q4 dose group and 0.5 in the 0.75q2 dose group. In CT subjects, bone age at baseline was moderately delayed by an average of ~1 year relative to chronological age in all dose groups. The mean change in bone age after 6 months of treatment was 0.7 years in all dose groups. Therefore, in both CT and naive subjects, the average rate of bone age

advancement was appropriate, indicating that improvements in growth rate were achieved without undue skeletal maturation.

Anti-GH Antibodies

Serum samples obtained at 3 month intervals were assayed for anti-GH antibodies, using Genentech's [redacted] assay. Four CT subjects had positive antibody titers at baseline; 6 CT subjects developed positive antibody titers during the course of the study. None of the naïve subjects had positive antibody titers at baseline; 14/26 naïve subjects developed positive antibody titers during the course of the study.

The maximum antibody titer observed at any time after baseline was 2.2 in both CT and naïve subjects. On average, once a CT or naive subject had a positive antibody titer, there was no trend for additional increase or decrease in the titer in that subject during the study period. Historically, antibodies suspected of being growth attenuating have not been observed with titers this low. All serum samples with positive antibody titers (>1.0) were assayed for binding capacity. No subject had a binding capacity value >2 mg/L. As expected when antibody titers are low, the majority of the samples with positive titers had binding capacities that were below assay limits.

Most importantly, the distribution of the 6 month annualized growth rates for antibody (+) and antibody (-) CT and naïve subjects were very similar. It is therefore highly unlikely that anti-GH antibodies attenuated the efficacy of Nutropin Depot during this study.

GH PK Data and IGF-I, IGFBP-3, and GHBP Data* (with implications for both efficacy and safety) *See Biopharmaceutics Review for more detailed description and analysis.

The PK profile of GH as well as the changes in concentrations of the related biological markers of rhGH activity (IGF-I, GHBP, and IGFBP-3) were investigated in 52 subjects at regular intervals during all treatment cycles (pre-dose and at 1, 7, 14 and 21 days post-dose for monthly injections, and pre-dose and at 1, 7 and 14 days post-dose for twice monthly injections). In addition, a subset of subjects who received doses of 0.75q4 and 1.5q4 underwent more intensive blood sampling (in particular during the first 2 days following dosing) for GH and IGF-I

levels following the first dose and for some subjects following the second dose as well.

GH PK Data

The mean GH serum concentration-time profiles for the 0.75q4, 1.5q4, and 0.75q2 dose groups were similar in the CT and naive subjects, approximately dose proportional, and reproducible during the course of the study (6 treatment cycles). In addition, the serum GH profiles from Day 0 to 14 post-dose after 0.75q2 administration were very similar to the same GH profiles after 0.75q4 administration.

Baseline mean serum GH concentrations ranged from 0.27 ng/ml to 1.7 ng/ml in all subjects. GH concentrations 24 hours post-dose (larger peak values were observed ~12 hours post dose) ranged from 14 ng/ml to 43 ng/ml, and were approximately dose proportional. Of note, ~50% of the $Gh_{\text{area under the curve (AUC) 0-28}}$ occurred during the first 2 days post-dose. GH levels returned to baseline ~2 weeks after dosing. As per the Agency's biopharmaceutics reviewer, the bioavailability of rhGH during the course of a month after a single SC injection of 1.5 mg/kg of Nutropin Depot was ~33% of the bioavailability of rhGH after daily SC injections of rhGH administered for 1 month (0.043 mg/kg/day = ~1.3 mg/kg/month) ($GH_{AUC0-28}$ after daily intravenous (IV) administration of rhGH for 1 month [projected] was determined as the gold standard; then $GH_{AUC0-28}$ after daily IV rhGH for 1 month {projected], daily SC rhGH for 1 month [projected] and Nutropin Depot SC monthly were compared). As per the Agency's biopharmaceutics reviewer, these was insufficient information presented in the submission to comment on the effect of the varying concentrations of injectate utilized in this study on the bioavailability of rhGH.
The correlation, if any, of GH_{AUC} and the annualized growth rates achieved in this study is discussed in the Biopharmaceutics Review.

GH levels 24 hours post-dose for each dose group in CT and naïve patients showed no increasing or decreasing trend during the course of the study (i.e., levels during cycle 1 were no different than levels during cycle 6). These results indicate that the initial-release phase of rhGH after repeated SC administration of Nutropin Depot was reproducible in children with GHD, and that GH disposition during the initial phase was not affected substantively by previous rhGH exposure (CT vs. naïve similar) nor by repeated dosing over 6 months. The remainder of the GH serum concentration-time profile was similar

as well during the course of the study (i.e., a return to baseline levels ~2 weeks post dosing), indicating that the sustained-release phase of rhGH after repeated SC administration of Nutropin Depot was reproducible as well, and that GH did not accumulate inappropriately over time.

IGF-I, IGFBP-3 and GHBP Data

Baseline serum IGF-I levels were, as expected, low in naïve subjects (range, 54 ng/ml to 102 ng/ml; lower limit of normal for 7 to 10 year old males is ~88-110 ng/ml) and were within the normal reference range in CT subjects. After the administration of Nutropin Depot, IGF-I values increased 2 to 8 fold, peaking ~1.5 days post-dose in the intensively sampled subset. Peak values usually did not exceed the upper limit of the normal reference range (~474-565 ng/ml in 7 to 11 year males). Increases were variable among subjects and not proportional to the dose of Nutropin Depot administered. The increases in IGF-I were generally larger (~2 fold) in the CT subjects compared with the naive subjects for unknown reasons, perhaps in part related to an increased capacity for IGF-I response in the CT subjects as a result of their prior rhGH treatment. IGF-1 values returned to baseline ~2 weeks after dosing. $IGF\text{-}I_{AUC0\text{-}28}$ did not correlate with growth rate.

During the course of the study (6 treatment cycles), peak IGF-I levels were similar for each dose group in CT and naïve patients, and IGF-I levels consistently returned to baseline values ~2 weeks after dosing. These results indicate that the IGF-I response was reproducible, and that subjects were not exposed to sustained inappropriately elevated IGF-I levels during the 6 month study period. The IGFBP-3 response was similar to the IGF-1 response; however, GHBP levels remained unchanged or declined during Nutropin Depot treatment.

8.1.2.4 Safety Results

Extent of Exposure

The 64 subjects with GHD who were enrolled in this study were treated an average of 0.42 years for a total of 27 subject-years of exposure.

Deaths

There were no deaths during the study.

Serious Adverse Events

One serious adverse event occurred during the study - otitis media complicated by vomiting and dehydration requiring hospitalization. It was not felt to be related to the study drug.

Adverse Events Leading to Withdrawal

As noted earlier in this review (Table 5), 7 subjects discontinued treatment because of an adverse event. Four subjects discontinued from the study because of injection site pain (see ahead to section on Injection Site-Related Adverse Events); 2 CT subjects, in the 1.5q4 dose group, discontinued after 1 and 2 doses, respectively, and an additional 2 naive subjects in the 0.75q4 dose group discontinued after each received four doses. In addition, 2 CT subjects in the 0.75q4 dose group, both with a history of hypoglycemia when GHD deficiency was originally diagnosed, experienced more frequent, clinically significant hypoglycemic episodes during the study. These patients were discontinued from the study and switched back to daily injections of rhGH because it was felt that the 0.75q2 dosage had resulted in unsatisfactory lower blood levels of rhGH, thereby predisposing the patients to more hypoglycemic episodes. A seventh subject was discontinued from the study because of the high likelihood of allergy (manifested by recurrent temporally related rash) to some component of Nutropin Depot. Of interest, the subject's serum was subsequently tested in vitro and no immunoglobulin E (IgE) antibodies with specificity to any of the components of Nutropin Depot, including microspheres, diluent, or rhGH, were detected.

Adverse Events Previously Associated with rhGH Therapy

1. None of the more severe but unusual adverse events associated with rhGH therapy (i.e. intracranial hypertension, proliferative retinopathy, slipped capital femoral epiphysis, hypercalcemia, gynecomastia or pancreatitis) occurred during this trial. In addition, no cases of leukemia were reported.

2. Hypothyroidism - Ten patients were being treated with L-thyroxine at baseline. No additional cases of hypothyroidism were unmasked by Nutropin Depot therapy.

3. Allergy - As discussed above, 1 child was discontinued from the study because of the high likelihood of allergy to some component of Nutropin Depot.

4. Arthralgia or myalgia was reported by 8 subjects. There were no reports of carpal tunnel syndrome.

5. Hyperglycemia - Patients with known diabetes mellitus were excluded from the study. Glucose metabolism was monitored by measurement of fasting and postprandial glucose and insulin levels, as well as hemoglobin A1C. Small increases in mean fasting blood glucose (FBG) levels were noted 24 hours post-dose (mean FBG ~75-85 mg% baseline and ~ 95-100 mg% 24 hours post-dose) in all 3 dose groups. Not surprisingly, these mild elevations in mean FBG levels 24 hours post-dose occurred simultaneously with the transient surge in serum GH 12-24 hours post-dose discussed earlier. However, FBG levels returned to baseline before the next dose of Nutropin Depot, and there were no significant changes in mean fasting or postprandial glucose or insulin levels, or mean hemoglobin A1C, noted after 6 months of Nutropin Depot therapy. See Table 9 below.

No subject developed diabetes mellitus during the study. Increased glucose and insulin levels were observed occasionally in individual subjects; however, these abnormalities were transient and did not persist. Subject 11-006, a 10 year old CT female in the 1.5q4 dose group, had elevated glucose levels (144, 151, and 130 mg/dL) 24 hours post-dose at Months 2, 3, and 4.?? Hemoglobin A1C was elevated at baseline (6.2%), but had decreased to 5.5% at the end of 6 months of Nutropin Depot therapy in this subject. Subject 9-002 in the 0.75q4 dose group was reported to have glycosuria on one occasion at Month 1 (24 hour post-dose) and hyperglycemia (24 hours post-dose) at Month 2. Nutropin Depot therapy was continued and no additional occurrences of hyperglycemia or glycosuria were noted during the remainder of the study.

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Table 9. [redacted]03-002 - Glucose Metabolism

	0.75q4		1.5q4		0.75q2	
	Baseline (n=19)	Month 6 (n=12)	Baseline (n=25)	Month 6 (n=18)	Baseline (n=20)	Month 6 (n=19)
Fasting glucose (mg/dL)	87±9	79±11	82±10	82±8	78±11	78±10
Postprandial glucose (mg/dL)	96±23	92±14	80±19	86±19	84±21	84±18
Fasting insulin (μU/mL)	5.8±5.6	6.9±3.8	3.0±2.1	3.8±3.6	3.8±3.1	4.1±3.7
Postprandial insulin (μU/mL)	25.3±21.0	23.9±20.3	11.5±10.9	13.1±10.4	17.3±14.8	19.1±28.1
Hemoglobin A1C (%)	5.7± 0.41 (n=13)	5.7± 0.49 (n=13)	5.9±0.44 (n=20)	5.4±0.42 (n=20)	5.8±0.38 (n=20)	5.4 ± 0.55 (n=20)

Adverse Events Related to Injection Site Reactions

Nutropin Depot was administered as a SC injection every 2 or 4 weeks using a 1 inch, 22-gauge needle and, later in the study, a 1 inch, 21 gauge needle. Parents and subjects were instructed to record observations of the injection sites daily and to report these observations to the investigator at monthly visits.

Table 10 below was compiled by this reviewer using datasets supplied by the sponsor; it reports the number/percentage of patients experiencing a given injection site reaction at least once during the study - for each dose group and for all dose groups combined. It is evident that the incidence of injection site reactions was extremely high during this study with no meaningful differences between dose groups. Sixty three of the 64 subjects treated with Nutropin Depot reported adverse events related to the injection site. As noted earlier, 4 of the 64 subjects discontinued treatment because of injection site events. The most frequent injection site reactions were pain post- injection, erythema and nodules with incidence rates of 92%, 89% and 87%, respectively (when all 3 dose groups are combined). The incidence of lipoatrophy was 33% for the entire cohort. The great majority of these injection site reactions were rated as mild to moderate in intensity. Pain during injection (32% overall incidence) was the injection site reaction most frequently rated as severe (application of EMLA cream or ice was used to minimize the discomfort during injection).

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Table 10. [redacted]03-002 - Number/% of Patients in Each Dose Group Experiencing Injection Site Reaction at Least Once

INJECTION SITE ADVERSE REACTION	All 3 dose groups combined n=63	0.75q4 n=19	1.5q4 n=24	0.75q2 n=20
PAIN POST INJECTION	58/92%%	19/100%	20/83%	19/95%
ERYTHEMA	56/89%	17/89%	20/83%	19/95%
NODULES	55/87%	18/95%	19/79%	18/90%
ITCHINESS	32/51%	10/53%	12/50%	10/50%
BRUISING	28/44%	9/47%	8/33%	11/55%
LIPOATROPHY	21/33%	8/42%	7/29%	6/30%
PAIN DURING INJECTION	20/32%	6/32%	6/25%	8/40%
EDEMA	8/13%	3/16%	0/0%	5/25%
WARMTH	8/13%	2/11%	3/13%	3/15%
REACTION	2/3%	1/5%	0/0%	1/5%
INDURATION	2/3%	1/5%	1/4	0/0%

Since many patients experienced multiple types of injection site reactions on multiple occasions, the total number of injection site reactions were compared with the total number of injections administered during the study. This is shown in Table 11. The ratio of total number of injection site reactions to total number of injections was 3/1 - a statistic which dramatically underscores the inordinately high incidence of injection site reactions after the administration of Nutropin Depot. This table also points out that pain during injection accounts for almost all of the 2% of injection site reactions rated as severe.

Table 11. Injection Site Reactions Compared with Total Number of Injections

TOTAL # OF INJCTNS	# OF INJCTN SITE REAX	# OF severe INJCTN SITE REAX
821	2034	47(2%)*

*44/47 = pain during injection

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Further issues regarding injection site reactions:

1) When it became apparent that there was a large discrepancy (~300) between the number of injections actually administered during this study (821) and the number of injections projected if each subject received 1 injection at each dosing (~500), this reviewer requested that the sponsor account for this discrepancy. Review of Case Report Forms reveals that the additional injections are primarily accounted for by the weight-driven dosage requirements of many patients mandating additional injections at each dosing, as well as the fact that several medical centers would not allow an injection volume >1 ml.

Reviewers Comment:

There is no evidence, therefore, that the subjects in this study elected to take more than the required number of injections to reduce the volume per injection and possibly the pain during injection.

2) In view of the remarkably high incidence of injection site-related adverse events after the administration of Nutropin Depot, the question arose as to whether there was a highly susceptible subgroup of GH deficient children sustaining the bulk of these adverse events. At the request of this reviewer, the sponsor recently performed a careful analysis of the naïve subjects who completed [redacted]03-004 (wherein injection procedures had been modified and optimized based on the experience obtained in [redacted]03-002) which did not reveal evidence for a susceptible subset (see ahead to [redacted]03-004 review and integrated summary of safety [ISS] for further details).

Other Adverse Events by Body System

Subjects were asked to report any adverse events or intercurrent illnesses at each monthly visit. Thirty one of the 64 subjects enrolled reported the occurrence of nausea, vomiting, fever, flu-like syndrome, or headache on at least one occasion during the study. These events were generally mild and short-lived, and occurred more than once in 12 of 31 subjects. In 15 of these patients (23% of all subjects), the onset of these complaints seemed to follow the administration of Nutropin Depot by 1-2 days. Results of physical examination, including funduscopic examinations to rule out intracranial hypertension, were unrevealing. Please refer to ISS for further incidence data generated by the sponsor at the request of this reviewer

regarding this group of "post-dosing" adverse events (collectively and individually).

Reviewer Comment:
The absolute number of post-dose events reported was higher than what has been observed historically in studies of similar pediatric subjects treated with daily injections of rhGH. It is possible that the more frequent contact with the investigator (every 4 weeks compared with every 3-4 months in previous studies) introduced a bias in reporting of events, but this is not entirely clear.

Physical examination and vital signs

No consequential changes occurred during the study.

Miscellaneous laboratory parameters

During the 6 month course of this study no consequential, clinically significant or consistent changes were observed in renal function, urinalyses, hematologic parameters, electrolytes, calcium, phosphate, alkaline phosphatase, lipids or liver function.

GH PK parameters and IGF-I levels with safety implications (see more detailed discussion of this data earlier in this review)

1) GH concentrations 24 hours post-dose ranged from 14 ng/ml to 43 ng/ml and were approximately dose proportional. Of note, ~50% of the $GH_{AUC0-28}$ occurred during the first 2 days post-dose. GH levels returned to baseline ~2 weeks after dosing. GH levels 24 hours post-dose and the remainder of the GH serum concentration-time profiles were very similar during each treatment cycle - for each dose group in CT and naïve patients. These results indicate that both the initial-release and sustained-release phases of rhGH after repeated SC administration of Nutropin Depot were reproducible in children with GHD, and that GH did not accumulate inappropriately over time.

2) Peak GH levels 12-24 hours post-dose seemed to correlate with the very modest, clinically insignificant, transient increase in FBG 24 hours post-dose.

3) After the administration of Nutropin Depot, baseline IGF-I values increased 2 to 8 fold, peaking 1.5 to 3 days post-dose. Peak values usually did not exceed the upper limit of the normal reference range. Increases were variable among subjects and not proportional to the dose of Nutropin Depot administered. IGF-1 values returned to baseline ~2 weeks after dosing. During the course of the study (6 treatment cycles), peak IGF-I levels were similar for each dose group in CT and naïve patients, and IGF-I levels consistently returned to baseline values ~2 weeks after dosing. These results indicate that the IGF-I response was reproducible, and that subjects were not exposed to sustained inappropriately elevated IGF-I levels during the 6 month study period.

8.1.3 Discussion

8.1.3.1 Efficacy Discussion

Naïve subjects

In this study, the mean 6 month annualized growth rate of growth hormone deficient patients naïve to rhGH therapy treated with Nutropin Depot was significantly greater than the mean pre-study growth rate and similar in both dose groups. Mean standardized height improved significantly as well and the rate of bone age advancement was appropriate in both dose groups, indicating that the improvements in growth were not accompanied by an undue advancement of bone age.

However, the mean 6 month annualized growth rate was significantly less than the mean annual growth rate achieved by well matched historical controls treated with daily injections of rhGH (mean delta=2.3 cm/yr, p=0.005). It is unlikely that noncompliance or problems with injection preparation or administration are explanatory factors in that all injections were reliably prepared and administered by health care providers at the sites where the study was conducted. It is well known that the growth velocity response of children with GHD after treatment with rhGH is inversely correlated with age at the onset of therapy. It is therefore important to note that the mean age of the naïve patients who received Nutropin Depot (~7) was slightly less than the mean age of the naïve patients who were treated with daily rhGH in the L0368g study (~8). Furthermore, in that 1.5q4 and 0.75q2 resulted in very similar mean annualized growth rates, the frequency of dosing does not appear to offer an explanation either.

On the other hand, as pointed out by this reviewer earlier, the sponsor failed to include diminished baseline growth velocity as an inclusion criteria and the baseline pre-treatment mean annualized growth rate in the naïve subjects treated with Nutropin Depot was greater than expected (~5.6 cm/yr). This raises the possibility that at least some of the subjects enrolled in this study were not truly growth hormone deficient (or were less severely growth hormone deficient than the subjects in the L0368g study); therefore, the mean response of this group of naïve patients after treatment with Nutropin Depot may have been attenuated.

The observed relative lack of efficacy after treatment with Nutropin Depot compared with daily injections of rhGH may also relate to the GH PK profile and GH-induced IGF-I response following the administration of Nutropin Depot. After the administration of Nutropin Depot, GH levels peak at ~12 hours (well above the normal range, ~20-100 ng/ml), in a dose proportional, reproducible manner, and subsequently progressively decline returning to baseline levels at ~2 weeks. In addition, 50% of $GH_{AUC0-28}$ after the administration of Nutropin Depot occurs in the first 2 days resulting in less GH exposure during the 12 or 26 days prior to the next dose. Furthermore, the bioavailability of rhGH during the course of a month after a single SC injection of 1.5 mg/kg of Nutropin Depot is ~33% of the bioavailability of rhGH after daily SC injections of rhGH administered for 1 month (0.043 mg/kg/day = ~1.3 mg/kg/month). As per the Agency's biopharmaceutics reviewer, there was insufficient information presented in the submission to comment on the effect of the varying concentrations of injectate utilized in this study on the bioavailability of rhGH. Moreover, it is not clear whether injection site location and/or the number of injections per dosing (usually 1, 2, or 3) impacted the bioavailability of rhGH. The correlation, if any, of GH_{AUC} and the annualized growth rates achieved in this study is discussed in the Biopharmaceutics Review.

As expected, baseline IGF-I levels were low or low normal in naïve subjects compared with age- and sex-matched normals. IGF-I levels peaked at ~1.5 to 3 days (2 to 8 fold increase well into the normal reference range), in a non-dose proportional but reproducible manner, and subsequently progressively declined returning to low or low normal baseline levels within 14 to 20 days of dosing. $IGF\text{-}I_{AUC0-28}$ did not correlate with growth rate. However, the importance of unsustained normalization of serum IGF-I levels must be interpreted cautiously. It is well established that IGF-I levels do not correlate with growth

velocity even after the administration of daily rhGH to growth hormone deficient children. Among other things, this lack of correlation may be related to noncompliance and/or intersubject variability and/or the greater importance of locally generated IGF-I in GH target tissues (as opposed to IGF-1 of hepatic origin which accounts for most of the IGF-I measured in serum) (Yakar, 1999).

CT subjects

In this study, as noted earlier, the mean annualized on-study growth rates are significantly less than the mean annualized pre-study growth rates in CT patients (delta=2.1 to 3.7 cm/yr). In the ITT sample, paired differences for all treatment groups are either highly statistically significant or borderline significant ($p<0.06$ or <0.08).

In an attempt to explain the relative lack of efficacy of Nutropin Depot compared with daily injections of rhGH in CT subjects, the sponsor suggests that the expected decline in response to rhGH (as catchup growth diminishes) may be a contributory factor. This reviewer disagrees! In the previously referenced study published by MacGillivray et al, the decline in annual growth rate during a 4 year course of therapy of children with GHD with daily injections of rhGH was 11.4 cm (year 1), 9 cm (year 2), 8 cm (year 3) and 7.5 cm (year 4). In this study, prior to switchover to Nutropin Depot, the mean duration of daily rhGH therapy in CT subjects was ~3 years. Therefore, one would project an annualized growth rate of ~7.5 cm/yr during the fourth year of therapy - which clearly exceeds the mean annualized growth rate of ~5 cm/yr observed in each dose group of CT subjects treated with Nutropin Depot. Interestingly, MacGillivray et al also found a similar significant difference (delta=1.5 cm/yr) in mean annual growth rate between year 3 and year 4 when rhGH (0.3 mg/kg/week) was administered daily and compared with the same amount of rhGH administered less frequently, TIW.

The sponsor notes further that the ~5 cm/yr mean annualized growth rate achieved with Nutropin Depot is more or less equivalent to the expected (50^{th} percentile) growth rate of age-matched (9.6 year old) normal children and adequate to maintain standardized height. Although this observation is correct, one must be cautious superimposing the growth rates of children with GHD (baseline and indeed after rhGH therapy) on a normative curve of growth velocities. Moreover, it does not change the fact (as noted above) that children treated with daily

injections of rhGH appear to grow better - even several years after the initiation of therapy. In other words, they are still "catching up".

As discussed above with regard to naïve subjects, it is unlikely that noncompliance (all study patients were injected by health care professionals), frequency of dosing (the responses to 1.5q4 and 0.75q2 were identical) or age (each subject served as his/her own control) help to explain the decreased efficacy of Nutropin Depot in CT patients. On the other hand, as also discussed above at length with regard to naïve patients, it is feasible that decreased rhGH bioavailability after Nutropin Depot administration compared with rhGH bioavailability after daily rhGH injections, unsustained normalization of serum GH and IGF-I levels following administration of Nutropin Depot, and disproportionate maximal exposure to rhGH in the 2 days following injection may be an explanatory factors.

Finally, as in the case of the naïve cohort, the failure to include diminished baseline pre-treatment growth rate (prior to the remote initiation of daily rhGH in the CT cohort) in the inclusion criteria may have led to enrollment of patients who were not truly GH deficient and therefore not as responsive to rhGH therapy. However, this is unlikely in view of the ~8 cm/yr mean annualized growth rate of the CT subjects during the ~third year of therapy with daily rhGH. In addition, as pointed out by the Agency's statistical reviewer, subjects less compliant on daily rhGH therapy (and therefore more GH deficient and more responsive to subsequent therapy with Nutropin Depot) may have been more likely to be enrolled in the CT cohort.

8.1.3.2 Safety Discussion

The 64 subjects with GHD who were enrolled in this study were treated an average of 0.42 years for a total of 27 subject-years of exposure.

Analysis of GH PK and IGF-I response data indicates that after repeated SC administration of Nutropin Depot, both the initial-release and sustained-release phases of rhGH and the rhGH-induced IGF-I response were reproducible in children with GHD, and that GH and IGF-I did not accumulate inappropriately over time.

None of the severe but unusual side effects associated with rhGH therapy were observed in this study. No subject developed diabetes mellitus, although transient elevations of glucose and

insulin were occasionally observed in individual subjects. Small increases in FBG levels were noted 24 hours post-dose (peak FBG ≤ 95-100) in all 3 dose groups which, not surprisingly, coincided with the transient surge in serum GH 12-24 hours post-dose. However, FBG levels returned to baseline before the next dose of Nutropin Depot, and there were no significant changes in mean fasting or postprandial glucose or insulin levels, or mean hemoglobin A1C, noted after 6 months of Nutropin Depot therapy.

In contrast to the very small incidence of injection site-related adverse events associated with daily injections of rhGH, the incidence of injection site reactions was extremely high during this study with no meaningful differences between dose groups. The ratio of total number of injection site reactions to total number of injections was 2.5/1! Sixty three of the 64 subjects treated with Nutropin Depot reported adverse events related to the injection site and, as noted earlier, 4 of the 64 subjects discontinued treatment because of injection site events. The most frequent injection site reactions were pain post-injection, erythema and nodules with incidence rates of 91%, 88% and 86%, respectively (when all 3 dose groups are combined). The incidence of lipoatrophy was 33% for the entire cohort. The great majority of these injection site reactions were rated as mild to moderate in intensity. Pain during injection (31% overall incidence) was the injection site reaction most frequently rated as severe. There was no evidence, however, that the subjects in this study elected to take more than the required number of injections to reduce the volume per injection and possibly the pain during injection.

Approximately 23% of subjects (all 3 dose groups combined) reported transient headache, nausea, vomiting, fever or flu syndrome at least once 1-2 days post dosing. This incidence contrasts with the rarity of similar post-dose phenomena in studies of similar pediatric subjects treated with daily injections of rhGH. Of course, since these latter children receive daily injections, it is much more difficult to discern what symptoms are possibly related to dosing. It is possible that the more frequent contact with the investigator in this study (every 4 weeks compared with every 3-4 months in previous studies) introduced a bias in reporting of events.

Finally, 2 CT subjects in the 0.75q4 dose group (both with a history of hypoglycemia when GHD deficiency was originally diagnosed) who experienced more frequent, clinically significant hypoglycemic episodes during therapy with Nutropin Depot, were discontinued from the study because it was felt that the 0.75q2

dosage had resulted in unsatisfactory lower blood levels of rhGH. This reviewer believes this explanation is very plausible and agrees with the decision of the sponsor not to further study or market the 0.75q4 dosage.

8.1.4 Conclusions

8.1.4.1 Efficacy

Nutropin Depot was clearly not as effective as daily injections of rhGH in stimulating growth in both naïve and CT patients. In naïve patients, the mean annualized 6 month growth rate achieved after 6 months of Nutropin Depot therapy (8.7 cm/yr) was significantly greater than the pre-study baseline annualized growth rate of these children (5.4 cm/yr), but was significantly less than the annual growth rate observed in a comparable group of children treated with daily injections of rhGH (11.0 cm/yr) in an earlier pivotal study performed by the sponsor. As noted earlier, the administration of rhGH TIW (0.3 mg/kg/week) has also been shown to be not as effective as daily injections of rhGH (identical weekly dosage) in naïve patients with GHD; interestingly, the difference in growth rate after the first year of therapy in that trial (2.6 cm/yr) is quite similar to the difference in annualized growth rate observed when Nutropin Depot therapy and daily injections of rhGH are compared (2.3 cm/yr). In CT patients, the mean 6 month annualized on-study growth rates were significantly less than the mean annualized pre-study growth rates in the same children treated with daily rhGH (delta=2.1 to 3.7 cm/yr). In that 1.5q4 and 0.75q2 resulted in very similar mean annualized growth rates in both naïve and CT subjects, the frequency of dosing does not appear to explain the decreased efficacy observed after Nutropin Depot therapy. More than likely, as discussed at length earlier, the diminished efficacy observed after treatment of naïve and CT children with Nutropin Depot relates to the GH PK profile and the GH-induced IGF-I response observed after Nutropin Depot administration (i.e., markedly decreased rhGH bioavailability after Nutropin Depot administration compared with rhGH bioavailability after daily rhGH injections, 50% of GH exposure in first 2 days after dosing, and the return to baseline levels of GH and IGF-I 2 weeks after dosing). This reviewer agrees with the sponsor's decision at that point in time to further study the efficacy of 0.75 2x/mo and 1.5 1x/mo of Nutropin Depot in [redacted]03-004 (a larger sample of naïve patients with GHD) and [redacted]03-003 (long term extension study).

8.1.4.2 Safety

The overall safety of Nutropin Depot in this study was satisfactory. However, injection site-related adverse events were extremely common - as many as 3 events for every injection administered. This contrasts with the minimal incidence of injection site reactions after daily injections of rhGH. In addition, ~20% (n=15) of the children in this study reported transient post-dose symptomatology (including headache, nausea, vomiting or fever) which contrasts as well with the minimal incidence of these phenomena after daily injections of rhGH. This reviewer agrees with the sponsor's decision at that point in time to eliminate the 0.75q2 dose group from subsequent studies, and to further evaluate the safety of 0.75 2x/mo and 1.5q 1x/mo in [redacted]03-004 (a larger sample of naïve patients with GHD) and [redacted]03-003 (long term extension study).

8.2 Study [redacted]03-004

8.2.1.1 Objectives

The objective of this 6 month, Phase III study was to demonstrate the safety and efficacy of 2 doses (1.5 1x/mo and 0.75 2x/mo) of Nutropin Depot in naïve, previously untreated children with GHD. Efficacy was assessed using 6 month annualized growth rates.

8.2.1.2 Study Design/Description of the Study

[redacted]03-004 was a Phase III, multicenter, open label, randomized, 6 month study which evaluated the efficacy and safety of Nutropin Depot in naïve, prepubertal children with GHD. Seventy four subjects with GHD and naive to rhGH treatment were enrolled and treated at 27 medical centers in the United States. Subjects were randomized centrally to 1 of the following 2 treatment groups: 1.5 1x/mo or 0.75 2x/mo (this constitutes a very minor change in dosing frequency compared with [redacted]03-002 where 1.5q4 and 0.75q2 were utilized). Subjects were dosed at home, usually by a parent or guardian. Subjects were seen in the clinic at 3 timepoints during the study: at baseline, at the end of 3 months, and at the end of 6 months. At the end of this 6 month study, subjects had the option of participating in the ongoing, open label study, [redacted]03-003, to assess the long-term safety and efficacy of Nutropin Depot.

8.2.1.3 Protocol

Protocol Amendments

The protocol was amended once on 19 November 1997 (Serial No. 024 submitted to IND [redacted]). The most significant component of that amendment eliminated the original intended efficacy outcome (i.e., [redacted]).

Materials and Methods

Subjects

Subject Selection

Seventy four subjects were randomized centrally to 1 of the 2 treatment groups: 1.5 1x/mo (n=36) or 0.75 2x/mo (n=38).

Inclusion Criteria

Inclusion criteria were identical to [redacted]03-002, excepting the elimination of criteria pertaining to CT children with GHD.

Exclusion Criteria

Exclusion criteria were identical to [redacted]03-002 excepting the exclusion of patients previously treated for GHD, and subjects with a history of panhypopituitarism/documented hypoglycemic episodes (2 such patients had more frequent hypoglycemic episodes while receiving 0.75q4 of Nutropin Depot during [redacted]03-002).

Method of Treatment Assignment

This was an open label study. Subjects were randomized centrally to 1 of the 2 dose regimens of Nutropin Depot, using random-permuted blocks (block size=4). The 2 treatment groups were randomly assigned within each block without stratification. Thirty subjects per group were required to complete 6 months of the study. Subjects who discontinued from the study before completing 6 months and before 35 subjects had been enrolled in either treatment group were replaced in the same dose group.

Study Treatment

Formulation

Nutropin Depot is a sustained-release formulation of somatropin (rhGH, Genentech). Sustained release of rhGH is achieved utilizing the [redacted] sustained-release depot delivery system described in review of [redacted]03-002. The diluent employed in [redacted]03-004 was the same CMC solution utilized in [redacted]03-002 after problems were encountered with the [redacted] solution diluent first used.

Dosage and Administration

The dose for each subject was calculated according to the individual's weight (baseline weight was used for the first 3 months of the trial and then weight at 3 month visit was used for rest of trial), and was administered as a SC injection. Subjects received 0.75 mg/kg of Nutropin Depot twice monthly or 1.5 mg/kg of Nutropin Depot monthly. Two dosage units of Nutropin Depot were used in this study, 18 mg of deliverable rhGH + 1.5 ml of CMC solution diluent (concentration 13 mg/ml) and 27 mg of deliverable rhGH + 1.5 ml of diluent (concentration 19 mg/ml). The very high incidence of injection site-related adverse events in [redacted]03-002 resulted in modification of drug administration procedures in [redacted]03-004 in an attempt to improve the tolerability of injections. Instead of 22 gauge, 1 inch needles, 21 gauge, ½ inch [redacted] needles were used in [redacted]03-004. Extensive instructions were prepared for at-home injections, including injection training by the clinic staff, an informational video provided to each subject's family, and detailed instructions for the resuspension of Nutropin Depot. Instructions on injection technique during injection and postinjection care of the injection site were also provided, along with a diagram of appropriate injection sites.

****If the total volume for any dose exceeded 1.2 ml, the dose was divided and administered at more than 1 injection site.**

Dosage Modification

The dose group of Nutropin Depot for each subject remained the same during the study. The dosage for each individual subject was adjusted for any change in body weight at the Month 3 visit.

Concomitant Therapy

Subjects with adrenocorticotrophic hormone (ACTH) deficiency could have received hydrocortisone at a dose that did not interfere with growth (physiologic replacement dose), and subjects with hypothyroidism could have received L-thyroxine. Dosage of either medication must have been stable for 3 months prior to the study.

8.2.1.4 Study Assessments

Screening/Pre-treatment Assessments

Screening assessments were made within 2 weeks of the first dose of Nutropin Depot to confirm subject eligibility and to establish baseline measurements. The assessments made were identical to those performed prior to [redacted]03-002, excepting modification of thyroid function panel to include TSH.

Assessments during Treatment

Efficacy Parameters

The primary efficacy endpoint was the 6 month annualized growth rate.

Secondary efficacy endpoints included height age, standardized height (height SDS), bone age and Bayley-Pinneau predicted adult height (PAH). The titer and binding capacity of anti-GH antibodies were determined as well.

Six month annualized growth rate, pre-study growth rate, standardized height, height age, bone age and anti-GH antibody titer/binding capacity were computed/determined as described for [redacted]03-002. Bayley-Pinneau PAH was calculated using the Bayley-Pinneau tables.

Height, weight, Tanner stage and anti-GH antibody measurements were performed after 3 and 6 months of Nutropin Depot therapy; bone age was reassessed after 6 months of therapy.

Safety Parameters

Safety assessments were made based on adverse event reports, as well as interim histories, physical examinations and laboratory studies after 3 and 6 months of Nutropin Depot therapy (exception: thyroid function was reassessed after 6 months of therapy).

PK Parameters and Biologic Markers (with both safety and efficacy implications)

Levels of GH, IGF-I, IGFBP-3 and GHBP were determined at baseline, after 3 months of Nutropin Depot therapy just prior to the next dose, and after completion of 6 months of therapy.

Subject Discontinuation

Criteria were identical to those described for [redacted]03-002.

8.2.1.5 Statistical Analysis

Efficacy Analysis

Primary Outcome Measure

The 6 month annualized growth rate estimates (means and 95% CI) are presented for each dose group and both dose groups combined (the rates were similar). A paired t-test was used to evaluate the change in annualized growth rate (i.e., the mean on-study 6 month annualized growth rate minus the mean pre-study annualized growth rate) for each dose group and both dose groups combined.

Reviewer Comment:
As pointed out by the Agency's statistical reviewer, no criteria for efficacy were defined in the protocol. The original protocol stated that an annualized growth rate of at least [redacted] cm/yr should be achieved; however, this objective was removed with the first amendment prior to the start of the trial. Further, it is not clear whether Nutropin Depot was expected to be comparable to or better than the comparator (daily injections of rhGH in Study L0368g [Nutropin AQ, NDA 20-522]). In addition, no measure of comparability (statistical comparison) is mentioned in the protocol. Data from Study L0368g demonstrate that the SD for an (efficacious) 6 month annual growth rate is 3.4 cm/yr (n=66). Based on that expected SD, the one-tailed lower limit of confidence of the mean was projected