

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 21-075**

**PHARMACOLOGY REVIEW(S)**

## REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

**KEY WORDS:** rhGH, [redacted] hGH, polylactide-coglycolide (PLG) copolymer, microspheres, IGF-1, Nutropin AQ

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**Division Name:** Metabolism and Endocrine Drug Products

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**Information to sponsor:** Yes ( ) No (X)

**Sponsor (or agent):** Genentech, Inc., 1 DNA Way, South San Francisco, California 94080-4990

Bulk somatropin is supplied by Genentech.

**Manufacturer of drug substance:** [redacted]

**Drug:**

**Code Name:** previously [redacted] rhGH

**Generic Name:** somatropin (rDNA origin)

**Trade Name:** Nutropin Depot [somatropin (rDNA origin) for injectable suspension]

**CAS Registry Number:** 12629-01-5

**Molecular Formula/ Molecular Weight:** 191 amino acid residues with a sequence identical to that of pituitary-derived human growth hormone. 22,125 daltons

**Relevant INDs/NDAs/DMFs:** IND [redacted] [redacted] rhGH); Nutropin NDAs 19-676, 20-168, Nutropin AQ NDA 20-522, Protropin NDA 19-107. DMF's [redacted]

**Drug Class:** Human Growth hormone (hGH) [somatropin (rDNA origin) for injectable suspension]

**Indication:** A sustained-release formulation of recombinant human growth hormone, indicated for the long-term treatment of patients with growth failure due to a lack of endogenous growth hormone secretion.

### Clinical formulation:

Nutropin Depot is a sustained-release formulation of somatropin. The formulation consists of micronized particles of rhGH embedded in biocompatible, biodegradable polylactide-coglycolide (PLG) microspheres packaged in vials as a sterile, white to off-white, preservative-free, free-flowing powder. Before administration, the powder is suspended in aqueous Diluent for Nutropin Depot.

The formulation consists of [redacted] rhGH [redacted] PLG copolymer, [redacted] zinc acetate, and [redacted] zinc carbonate. The dry powder is suspended in sterile Nutropin Depot Diluent comprised of [redacted] carboxymethylcellulose, [redacted] sodium chloride, and [redacted] polysorbate 20. The microspheres have an average particle diameter of approximately [redacted] and contain micronized particles of somatropin embedded in the polymer matrix. The Nutropin Depot microspheres are packaged in sterile vials as a sterile, dry, free-flowing powder. Before administration, the microspheres are hydrated by suspending them in an aqueous diluent. [Zinc is added to the formulation to complex and stabilize the rhGH both during formulation and release.]

Each 13.5 mg 3 cc single-use vial of Nutropin Depot contains 13.5 mg somatropin, 1.2 mg zinc acetate, 0.8 mg zinc carbonate, and 68.9 mg PLG.

Each 18 mg 3 cc single-use vial of Nutropin Depot contains 18 mg somatropin, 1.6 mg zinc acetate, 1.1 mg zinc carbonate, and 91.8 mg PLG.

Each 22.5 mg 3 cc single-use vial of Nutropin Depot contains 22.5 mg somatropin, 2.0 mg zinc acetate, 1.4 mg zinc carbonate, and 114.8 mg PLG.

Each dosage size contains an overage of rhGH microspheres to assure delivery of labeled contents.

Each 1.5 mL single-use vial of Diluent for Nutropin Depot contains 30 mg/mL

carboxymethylcellulose sodium salt, 1 mg/mL polysorbate 20, 9 mg/mL sodium chloride, and sterile water for injection; pH 5.8-7.2.

**Route of administration:** SC injection

**Proposed clinical protocol or Use:** The Nutropin Depot dosage and administration schedule should be individualized for each patient.

**Once-Monthly Injection**—It is recommended that an SC injection at a dosage of 1.5 mg/kg body weight be administered on the same day of each month. Dosages above the recommended once-monthly regimen have not been studied in clinical trials.

**Twice-Monthly Injections**—It is recommended that an SC injection at a dosage of 0.75 mg/kg body weight be administered twice each month on the same days of each month (e.g., Days 1 and 15 of each month). Dosages above the recommended twice-monthly regimen have not been studied in clinical trials.

**Disclaimer – use of sponsor's material:** Note some material may be taken directly from sponsor's submission.

**Introduction and drug history:** The protein somatotropin, is synthesized by a specific laboratory strain of *E. coli* as a precursor consisting of the rhGH molecule preceded by the secretion signal from an *E. coli* protein.

This NDA describes a sustained-release form of the currently marketed Genentech somatotropin product, Nutropin AQ® [somatotropin (rDNA origin) injection], utilizing [redacted] a [redacted] The technology consists of biocompatible, biodegradable microspheres formulated from poly D/L lactide co-glycolide (PLG). This polymer has a history of safe human usage in suture material, bone plates, and other sustained release drugs. Nutropin Depot is packaged in vials as a sterile, white to off-white, preservative-free, free-flowing powder. Before administration, the powder is suspended in aqueous Diluent for Nutropin Depot.

After subcutaneous injection of the suspension, the protein is released from the microspheres into the subcutaneous space and absorbed. Ultimately, the microspheres undergo hydrolysis into small, naturally occurring molecules (lactic acid and glycolic acid), which are completely metabolized by the body.

**Studies Reviewed Within This Submission**

**Review Page**

Pharmacology:

4

Growth Hormone

Genentech Ref. 98-186-1301:

5

GH Dosing in the Rat: Effects of Dose Pattern on Growth

ADME Studies:

7

[redacted] Ref. 03-02:

Two-Month Pharmacokinetic Study with [redacted] Human Growth Hormone in Rhesus Monkeys

[redacted] Ref. 03-04:

14

Pharmacokinetic and Pharmacodynamic Study of [redacted] Human Growth Hormone (hGH) PL50 Formulation in Juvenile Rhesus Monkeys

[redacted] Ref. 03-05:

21

Pharmacokinetic and Pharmacodynamic Study of [redacted] Human Growth Hormone (hGH) PL500 Formulation in Juvenile Rhesus Monkeys

[redacted] Ref. PD-03-11:

28

Summary of In Vivo Evaluations of Selected [redacted] rhGH (Nutropin Depot) Lots of Differing Process Scale Manufacture in the Rat

**Studies Reviewed Within This Submission**

	<u>Review Page</u>
Genentech Ref. 99-046-0750: Nutropin Depot Nonclinical ADME Species Comparisons: Pharmacokinetics, InVivo/In Vivo Correlations and Safety Factors	29
<u>Toxicology Studies</u>	32
[redacted] hGH Ref. AT-03-05: Three-Month Toxicokinetic Study with [redacted] Human Growth Hormone in Rhesus Monkeys	32
<u>Immunogenicity</u>	
[redacted] Ref. AT-03-08: Immunogenicity Study of [redacted] Human Growth Hormone in Transgenic Mice Expressing rhGH	44
<u>Diluent</u>	
[redacted] Ref. AT-03-09: An Acute Local Tolerance Study of [redacted] Vehicles Administered Subcutaneously to Rabbits	46
<u>PLG Microspheres</u>	
[redacted] Ref. AT-07-01: An Acute Local Tolerance Study of [redacted] Formulations RG 502H [redacted] and 10K PLGA 50:50 [redacted] Administered Subcutaneously to Rabbits	48

**Studies Not Reviewed Within This Submission:**

[redacted] (hGH) Tolerance Study Ref. AT-03-06: A Subcutaneous and Intramuscular Tolerance Study Following A Single dose of [redacted] Human Growth Hormone (hGH) in Rabbits (an acute, subchronic, local tolerance study) [See Pharm. Review of IND [redacted], 3 Jul 96 p.7]	
<u>PLG Microspheres</u>	
[redacted] Ref AT-07-02: Chronic Subcutaneous Local Tolerance of Poly(L-lactic acid) and Poly (D,L-lactide-co-glycolide) Microspheres and Discs in Rats [See Pharm. Review of IND [redacted] 3 Sep 92 p. 2]	
<u>I.V. Growth Hormone</u>	
[redacted] Ref. [redacted] 03-03: Intravenous Pharmacokinetic Study with Human Growth Hormone (hGH) in Rhesus Monkeys [See Pharm. Review of IND [redacted] 3 Jul 96 p. 7]	

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## PHARMACOLOGY

**Mechanism of Action:** The mechanism of action is the same as that of the naturally occurring growth hormone. Nutropin Depot treatment stimulates longitudinal bone growth and elevates insulin-like growth factor-1 (IGF-1) levels in a manner analogous to that observed with daily Nutropin [somatropin (rDNA origin) for injection] treatment.

Actions that have been demonstrated for hGH include: Tissue Growth (skeletal, cell, organ), Protein Metabolism, Carbohydrate Metabolism, Lipid Metabolism, Mineral Metabolism, and Connective Tissue Metabolism.

**Drug Activity Related to Proposed Indication:** Nutropin Depot is a sustained release formulation of somatropin designed to be administered by subcutaneous (SC) injection once or twice monthly. Following the injection, bioactive rhGH is released from the microspheres into the SC environment initially by diffusion, followed by both polymer degradation and diffusion. Once released into the SC space the rhGH is believed to be absorbed, distributed, and eliminated in a manner similar to somatropin formulated for daily administration.

### Summary of pharmacology:

The nonclinical information contained herein adds to an extensive experience with an understanding of the nonclinical pharmacology/toxicology/ADME properties of both endogenous or pituitary-derived and recombinant hGH, as well as several decades of clinical experience with hGH. Complete reports for the studies performed using rhGH products formulated for daily administration have been previously submitted to NDA 20-168 (9 July 1993) and NDA 20-522 (9 November 1994), and are not duplicated in this NDA.

### SAFETY PHARMACOLOGY

[From Sponsor's Vol. 1.1 Item 5 Pharmsum - 6]

#### Summary of Nonclinical Pharmacology Studies with Nutropin Depot

Study No.	Study Type	Species/ Strain	No/ Sex/ Group	Route of Admin.	Dose <sup>b</sup> (mg/kg)	Lot No.	Comments
88-188-1301 <sup>a</sup>	Growth	Rat/Hypox	6/F	SC	0.2	486	Dose-dependent increase in body weight and tibial width with Nutropin Depot. Potency less than rhGH given by osmotic pump or twice daily injection.
					1.0	1148B/	
					5.0	E9038AX M3 RD874	
-03-02 <sup>c</sup>	PK/PD	Monkey/immature	4/M	SC	21	0004	All [redacted] rhGH formulations stimulated increases in IGF-I and IGFBP-3 that were greater and more prolonged than rhGH given by daily injection. A single injection of [redacted] rhGH (Lot No. 0019) produced plasma profiles of IGF-I and IGFBP-3 that were more similar to a constant infusion of rhGH.
					23	0019	
					24	0022	
					25	0028 94-154-17A-D	
03-05 <sup>d</sup>	Toxicokinetic	Monkey/immature	4/M	SC	1.5	0081a	[redacted] rhGH stimulated dose-dependent increases in IGF-I and IGFBP-3 that were greater and more prolonged than rhGH given by daily injection. Similar IGF-I and IGFBP-3 responses were observed after repeat injection over 3 months.
					7.5	0081c	
					0.83 <sup>e</sup>	85-029-169	

Abbreviations: F = Female; Hypox = Hypophysectomized; SC = Subcutaneous; PK = Pharmacokinetic; PD = Pharmacodynamic.

<sup>a - Depot</sup>  
 Nutropin Depot was administered as a single SC injection. Nutropin AQ™ was administered by SC injection once or twice a day or by a SC infusion pump.

<sup>c-, d- Disregard</sup>  
 The 0.63 mg/kg dose was Nutropin administered by SC injection 3 dose/wk x 4 wks.

The general pharmacological properties of growth hormone are well known and will not be reviewed here.

### Pharmacology

Preclinical studies were performed to assess efficacy and safety of Nutropin Depot™, and are summarized as follows:

#### Growth Hormone

#### **GH Dosing in the Rat: Effects on Dose Pattern on Growth:**

Genentech, Inc. Genentech Ref. 98-186-1301. Vol. 1.1 (T5) 98-186-1301

Q.A. - Non-GLP Study Dates: 3-12 Aug 98.

Lots: Nutropin Depot Lot 0486; Nutropin AQ Lot 114BB/E9038AX

This study was a non-GLP study ( cursory review only) carried out by Genentech, Inc. in order to directly compare whole body growth responses of different dosing patterns of Nutropin AQ to Nutropin Depot in hypophysectomized rats.

**Dose:** Each rat received either placebo or 0.2, 1.0 or 5.0 mg/kg/day or equivalent dose of Nutropin.

Groups 1-7

**No. Animals:** 7 groups of 6 rats each

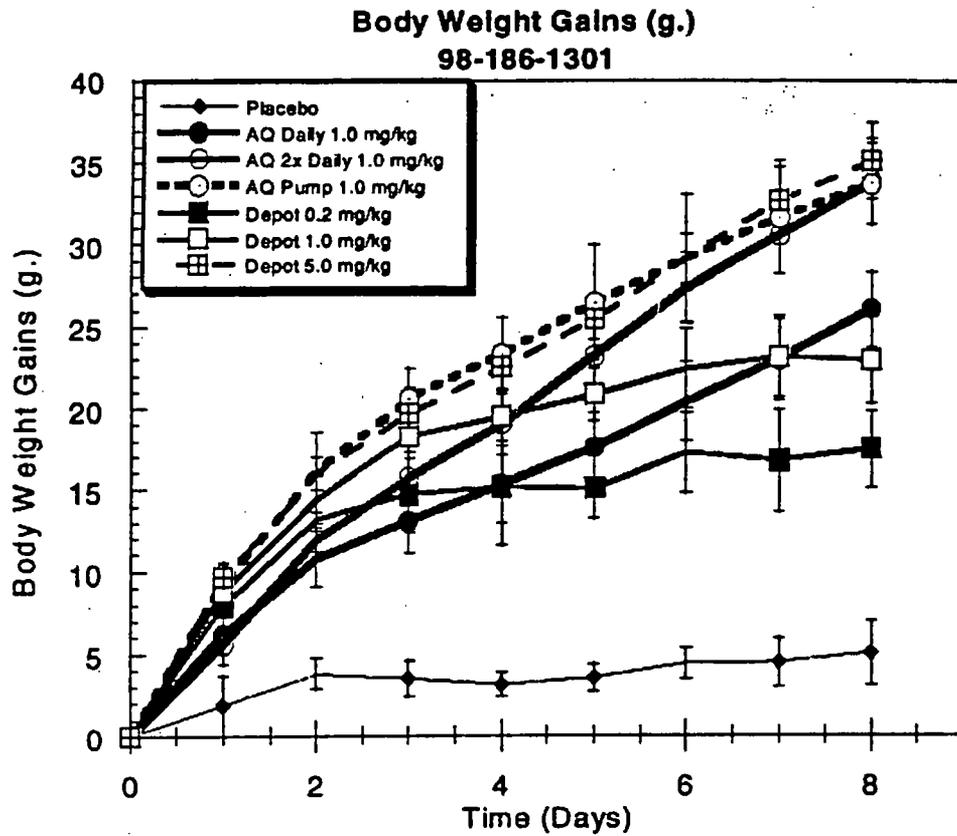
### Results

[Sponsor's Vol. 1.1 (T5) 98-186-1301 Item 5 p.10]

## **Serum hGH and IGF-1 Levels**

<b>Nutropin (mg/kg/day)</b>	<b>Serum hGH (ng/ml)</b>	<b>Serum IGF-1 (ng/ml)</b>
Placebo	LTS	73.8±34.5
<b>AQ</b>		
Daily 1.0	0.24±0.1 <sup>a</sup>	171.1±86.5 <sup>a,c</sup>
2x Daily 1.0	0.42±0.3 <sup>a</sup>	276.1±66.3 <sup>a</sup>
Pump 1.0	51.50±34.9 <sup>a</sup>	238.6±61.3 <sup>a</sup>
<b>Depot</b>		
0.2	1.39±0.0 <sup>a</sup>	88.9±46.1
1.0	1.23±1.5 <sup>a</sup>	170.0±53.4 <sup>a,c</sup>
5.0	100.3±52.0 <sup>b</sup>	334.2±40.1 <sup>a,b</sup>

Data are represented as Means  $\pm$  SD and were considered significant where  $P < 0.05$  using a Duncan's Multiple Range Test. a  $p < 0.05$  v. placebo, b  $p < 0.05$  v. all groups; c  $p < 0.05$  v. Nutropin AQ Pump.  
 [Sponsor's Vol. 1.1 (T5) 98-186-1301, Item 5 p 8]



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[From Sponsor's Vol. 1.1 (T) 98-186-1301 Item 5 p. 9]

## Relative Organ Weight (% of Body Weight)

Nutropin (mg/kg/day)	Body Wt. (g.)	Epiphy. ( $\mu\text{m}$ )	Liver	Heart	Kidney	Spleen	Thymus
Placebo	93.9 $\pm$ 3.5 <sup>a</sup>	213.7 $\pm$ 8.4 <sup>a</sup>	4.1 $\pm$ 0.3	0.37 $\pm$ 0.03	0.69 $\pm$ 0.04	0.21 $\pm$ 0.03	0.28 $\pm$ 0.02 <sup>a</sup>
<b>AQ</b>							
Daily 1.0	115.2 $\pm$ 6.0	438.7 $\pm$ 28.8	4.0 $\pm$ 0.1	0.35 $\pm$ 0.03	0.71 $\pm$ 0.04	0.26 $\pm$ 0.02	0.34 $\pm$ 0.04
2x Daily 1.0	122.7 $\pm$ 5.3 <sup>d</sup>	473.1 $\pm$ 25.4 <sup>de</sup>	4.1 $\pm$ 0.1	0.38 $\pm$ 0.05	0.74 $\pm$ 0.04	0.29 $\pm$ 0.03	0.36 $\pm$ 0.03
Pump 1.0	122.8 $\pm$ 3.0 <sup>d</sup>	427.8 $\pm$ 31.7	4.3 $\pm$ 0.3	0.37 $\pm$ 0.04	0.71 $\pm$ 0.05	0.33 $\pm$ 0.07 <sup>b</sup>	0.43 $\pm$ 0.06 <sup>d</sup>
<b>Depot</b>							
0.2	102.6 $\pm$ 4.1 <sup>c</sup>	341.0 $\pm$ 33.3 <sup>c</sup>	4.3 $\pm$ 0.3	0.37 $\pm$ 0.03	0.74 $\pm$ 0.05	0.24 $\pm$ 0.02	0.39 $\pm$ 0.05 <sup>d</sup>
1.0	108.0 $\pm$ 5.3 <sup>c</sup>	389.7 $\pm$ 48.1 <sup>c</sup>	4.3 $\pm$ 0.2	0.41 $\pm$ 0.03 <sup>d</sup>	0.75 $\pm$ 0.07 <sup>b</sup>	0.25 $\pm$ 0.02	0.46 $\pm$ 0.05 <sup>d</sup>
5.0	120.0 $\pm$ 4.1	485.8 $\pm$ 16.9 <sup>de</sup>	4.9 $\pm$ 0.3 <sup>b</sup>	0.39 $\pm$ 0.03	0.78 $\pm$ 0.04 <sup>bde</sup>	0.32 $\pm$ 0.03 <sup>b</sup>	0.45 $\pm$ 0.04 <sup>d</sup>

Data are represented as Means  $\pm$  SD and were considered significant where  $P < 0.05$  using a Duncan's Multiple Range Test. *a*  $p < 0.05$  v. all groups; *b*  $p < 0.05$  v. Placebo; *c*  $p < 0.05$  v. all Nutropin AQ treated groups; *d*  $p < 0.05$  v. Nutropin AQ Daily; *e*  $p < 0.05$  v. Nutropin AQ Pump.

**Summary:** Statistically significant increases were noted in body weight, bone growth and thymus size without affecting the size of other organs in rats treated with twice daily injections of Nutropin AQ. Rats infused with Nutropin via pump or Nutropin Depot showed increases in liver, spleen and kidney size as well as affecting whole body growth parameters. Thus, it is suggested that in hypophysectomized rats, Nutropin AQ, delivered continuously via either osmotic minipump or in a Nutropin Depot is effective in increasing body weight and bone growth, as well as that of organs associated with elevated IGF-1 levels

## PHARMACOKINETICS/TOXICOKINETICS

### Two- Month Pharmacokinetic Study with [redacted] Human Growth Hormone in Rhesus Monkeys:

[redacted] -03-02. Total IGF-I analyzed by Genentech, Inc.; IGF-binding protein 3 (IGF-BP3) analyzed by [redacted] hGH and antibody assays were conducted by [redacted] Histopathological evaluation of injection sites was performed by [redacted] Study initiated 9 Mar 95. Q.A. - Report and data by [redacted] Vol. 1.5 [redacted] 03-02 (T6) Item 5 p.1

**Formulation 2:** Lot 0019 - contained [redacted] hGH:Zn complex, [redacted] zinc carbonate, and [redacted] PLG Copolymer with hydrophilic end groups.

[redacted] Vehicle: Lot 0026 - contained [redacted] w/v carboxymethylcellulose, sodium salt, low viscosity (CMC); [redacted] Tween 20 (polyoxyethylenesorbitan monolaurate, in [redacted] Sodium Chloride for Injection, USP.

Human Growth Hormone (hGH) dosing solutions: Lots 94-154-17A, 94-154-17B, 94-154-17C, 94-154-17D.

Osmotic Pump: [redacted] Model 2ML4, Lot 044302.

[A Preliminary Summary of this study was reviewed under IND [redacted] [3 Jul 96 p. 4]. Portions of that review have been repeated here for completeness.]

Purpose:

A pharmacokinetic study in juvenile rhesus monkeys (age 13 to 27 mo. wt. 2.8 – 3.6 kg) was performed for the purpose of evaluating three [ ] hGH formulations when administered as a single subcutaneous injection to juvenile male rhesus monkeys (to mimic a juvenile human population).

Based on the pharmacokinetic/pharmacodynamic performance and basal tissue reaction characterized, the [ ] hGH formulation using [ ] PLG Copolymer with hydrophilic end groups (**Formulation 2**) was selected as the leading candidate for clinical development.

**NOTE:** Since **Formulation 2 was selected for clinical development**, this review of the final study will concentrate on Formulation 2 rather than on the other formulations tested.

Dose and Administration:

Dose volume was 1.2 mL except for the daily SC group (0.5 mL daily for 28 days). The [ ] osmotic pump was set to deliver ca 2.3 µL/hour for 28 days. All SC injections were made into the dorsal cervical region of 4 monkeys per group (3 for vehicle).

Blood samples were collected at various time points for analyses of hGH, total IGF-I and IGF-BP3 serum concentrations. Antibody titer was also determined.

SC injection sites were collected at the end of the study.

DOSE Chart [Sponsor's Table - from IND [ ] Pharm. Review dtd. 3 Jul 96 p. 4]:

Treatment group designations and numbers of animals were as follows:

Treatments	Dose Regimen	hGH Dose (mg/dose)	hGH Dose Conc (mg/mL)	Dose Vol (mL/dose)	# animals
[ ] hGH	single, Day 1	24	20	1.2	4
hGH solution	single, Day 1	24	20	1.2	4
hGH solution	28 daily	0.86	1.71	0.5	4
hGH solution	single, Day 1	3.6	7.2	0.5	4
hGH solution	28-day pump	20.4	13.2	1.55	4
[ ] hGH Vehicle	single, Day 1	0	0	1.2	3

24 mg hGH is contained in 160 mg [ ] hGH.

Dose Solution Analysis:

HGH dosing solutions determined by [ ] were slightly different from intended:

Single SC injection = 21.57 mg hGH/mL

Daily SC injection = 1.64 mg hGH/mL

Pump loading = 11.21 mg hGH/mL

SC injection for osmotic pump group = 6.87 mg hGH/mL

Results:

**Note:** [ ] designated the Day of initiation of treatment as Day 1 for in-life purposes. This pharmacokinetic study report, however, designates the day of initiation of treatment as day 0, and, therefore, all sampling points for hGH, total IGF-I, IGF-BP3, and anti-hGH antibody determination in this report are shown as one day earlier than in the in-life report. Thus, there may be a difference in reporting days for the IND and NDA.

Body Weights and Cumulative Body Weight Gains: No apparent drug-related changes.

Food Consumption: No apparent drug-related changes.

HGH:

All [ ] formulations showed an initial burst of ca 24-36 hours followed by a sustained release phase.

Formulation 2 produced blood levels of ca 10 ng/ml hGH until Day 16 after which mean levels of 2-6 ng/mL were seen through Day 55 followed by a diminished release which terminated after 9 weeks. Mean values for  $AUC_{0-last}$  were  $550 \pm 167$  ng day/mL,  $AUC_{0-2day}$   $200 \pm 53$  ng day/mL, and  $C_{max}$   $280 \pm 105$  ng/mL (normalized to 7.5 mg hGH/kg). For the initial burst, Formulation 2 showed somewhat lower  $AUC_{0-last}$ ,  $AUC_{0-2day}$ , and  $C_{max}$  values than either Formulations 1 or 3. Similarities existed between all three [ ] hGH formulations with respect to bioavailability and cumulative release. The mean cumulative hGH release for Formulations 1, 2, and 3 was  $111 \pm 29\%$ ,  $86 \pm 26\%$  and  $104 \pm 15\%$ , respectively. Bioavailability (F) ranged from 51-66% when it was estimated based on a IV study that gave 158.88 ng day/mL of AUC when normalized for a nominal dose of 3.525 mg hGH (Study [ ] 03-05).

Total IGF-I

[ ] hGH formulations produced an increase in total IGF-I levels. The osmotic pump group and the [ ] hGH groups exhibited higher levels of total IGF-I than the daily SC group, which received an equivalent amount of hGH as the [ ] hGH groups.

Formulation 2 showed elevated levels of total IGF-I between Days 3 and 25 in the range of [ ] ng/mL, with a mean of 732 ng/mL, and approached the pre-dose concentration (365 ng/mL on Day 31 with a concentration of 258 ng/ml).

The [ ] Vehicle control showed average total IGF-I levels in the range of [ ] ng/mL Days 0-28. The single SC group produced average total IGF-I levels in the range of [ ] ng/mL Days 0-10. Daily hGH administration did not produce a significant elevation in IGF-I level. In general the SC + osmotic pump group produced average total IGF-I levels in the range of [ ] ng/mL Days 5-31.

IGF-BP3 [Insulin like Growth Factor Binding Protein 3 – major circulating IGF carrier protein]

Formulation 2 produced a peak mean concentration of 6565 ng/mL at 48 hours. Concentrations ranged from [ ] Days 3-28. The range was lower ( [ ] ng/mL ) from days 31-55.

For the SC group, IGF-BP3 ranged from [ ] ng/mL Days 1-27 followed by baseline concentrations in the range of [ ] until Day 55.

The SC + osmotic pump group had an initial peak of 4811 ng/mL at Day 4 and a sustained phase of ca [ ] ng/mL Days 5-28.

Anti-hGH antibodies

Only one of the Formulation 2 monkeys had quantitatively detectable antibodies (Day 23 until end of study). None of the hGH solution monkeys developed detectable antibodies. [3 Formulation 1, and 2 Formulation 3 animals developed antibodies.]

Injection sites

On Day 3 injection sites were noted to be swollen in all Formulation 2 animals. At Day 5 swollen injection sites were present that persisted through Day 8. At Day 11 the swollen areas were noted as hard non-irritating enlargements. Enlargements for Formulation 2 monkeys decreased to an unobservable size between Days 29 and 35. [The sponsor indicates that these enlargements are consistent with the physical properties of [ ] hGH formulations that congeal following subcutaneous deposition and regress with time.]

At Day 60/61 only 1 of 4 Formulation 2 injection sites (ca 4 x 0.1 mm) was identified histologically. A few small cystic spaces (mostly < 100  $\mu$ m in diameter) were surrounded by a mild granulomatous inflammatory reaction with the presence of small amounts of hGH immunoreactive material. No local fibrosis was seen at the injection site.

Pharmacokinetic Analysis of hGH in Rhesus Monkeys: [ ] hGH Formulation 2 vs. Single SC, Daily SC and SC + Osmotic Pump

[Excerpted from Sponsor's Table 3 Vol. 1.5 [ ] 03-02 (T6) Item 5 p. 26]

	Formulation 2 Avg ± SD	Single SC Avg ± SD	28 Daily SC Avg ± SD	Single SC plus 28 day Pump Avg ± SD
Body Wt. Kg <sup>1</sup>	3.0 ± 0.34	3.30 ± 0.36	3.05 ± 0.44	3.18 ± 0.43
Dose, mg <sup>2</sup>	24.00 ± 0.00	25.88 ± 0.00	0.82 ± 0.00	20.77 ± 0.00
AUC <sub>0-last</sub> , ng•day/mL	550 ± 167	892 ± 41	33 ± 6	548 ± 92
AUC <sub>0-day2</sub> , ng•day/mL	200 ± 53	736 ± 165		138 ± 13
C <sub>max</sub> , ng/mL	269 ± 83	2050 ± 405	176 ± 59	556 ± 116
T <sub>max</sub> , day	0.44 ± 0.04	0.11 ± 0.03	0.07 ± 0.02	0.10 ± 0.04
C <sub>max</sub> , normalized <sup>3</sup>	280 ± 105	1929 ± 168		635 ± 136
C <sub>avg</sub> , ng/mL <sup>4</sup>	7.89 ± 3.25			14.92 ± 3.65
C <sub>avg</sub> , normalized <sup>5</sup>	8.07 ± 3.07			16.88 ± 3.38
Cumulative Release, % <sup>6</sup>	86 ± 26	129 ± 6		99 ± 17
F, % <sup>7</sup>	51 ± 15	76 ± 4	88 ± 15	59 ± 10

<sup>1</sup> Body Weight = Day 0.<sup>2</sup> Dose: Formulation 2 received 160 mg/1.2 mL of [ ] hGH, containing 24 mg hGH.

Single SC received 1.2 mL of 21.57 mg/mL solution.

28 Daily SC received 28 daily 0.5 mL SC injections of 1.64 mg/mL solution.

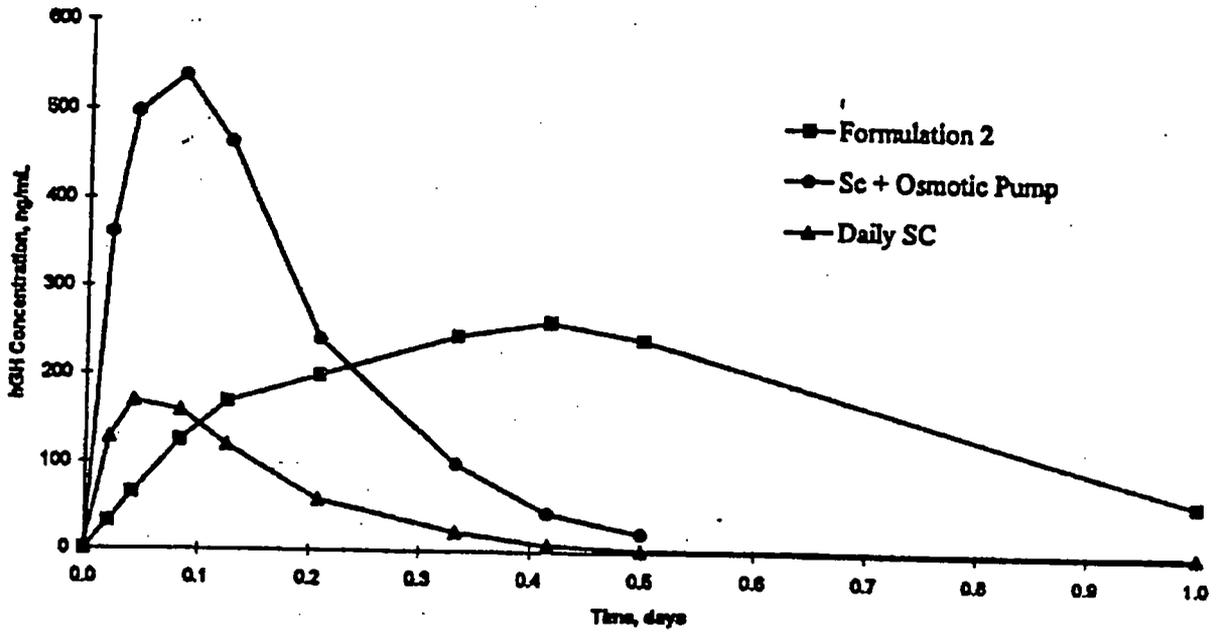
Single SC plus 28 day pump received single 0.5 mL SC injection of 6.87 mg/mL solution and 11.21 mg hGH/mL solution, release rate 2.3 µL/hr for 28 days.

<sup>3</sup> C<sub>max</sub>, norm = Normalized to 7.5 mg hGH/kg body weight.<sup>4</sup> C<sub>avg</sub> = C<sub>avg</sub> was determined by averaging the hGH concentrations of the steady state.<sup>5</sup> C<sub>avg</sub>, norm = Normalized to 7.5 mg hGH/kg body weight.<sup>6</sup> Cum Release = Based on 16 ng•day/mL of AUC @ 2.5% release/day and 24 mg of [ ] hGH dose.<sup>7</sup> Bioavailability (F) = Based on the monkey I.V. study [ ] Study [ ] (03-03): 158.88 ng•day/mL AUC @ 3.525 hGH dose.

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[Sponsor's Vol. 1.5 03-02 (T6) Item 5 p. 30]

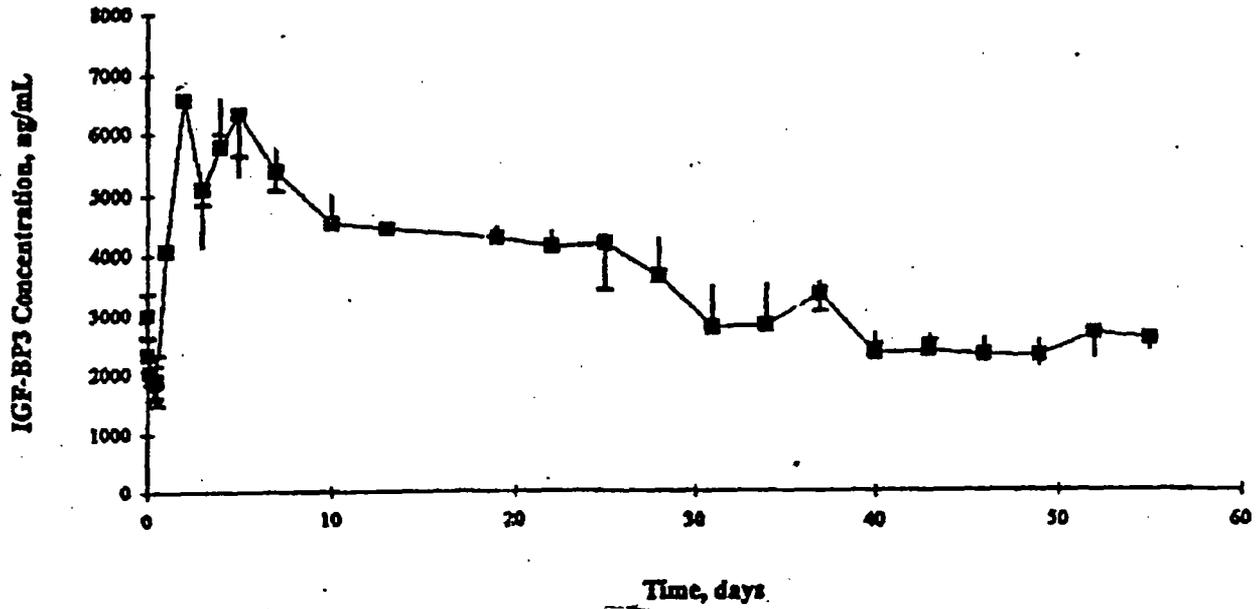
Mean hGH Serum Profiles in Rhesus Monkeys:  
hGH Formulation 2 vs. SC + Osmotic Pump and Daily SC



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## IGF-BP3 Serum Profiles in Rhesus Monkeys: [redacted] hGH Formulation 2



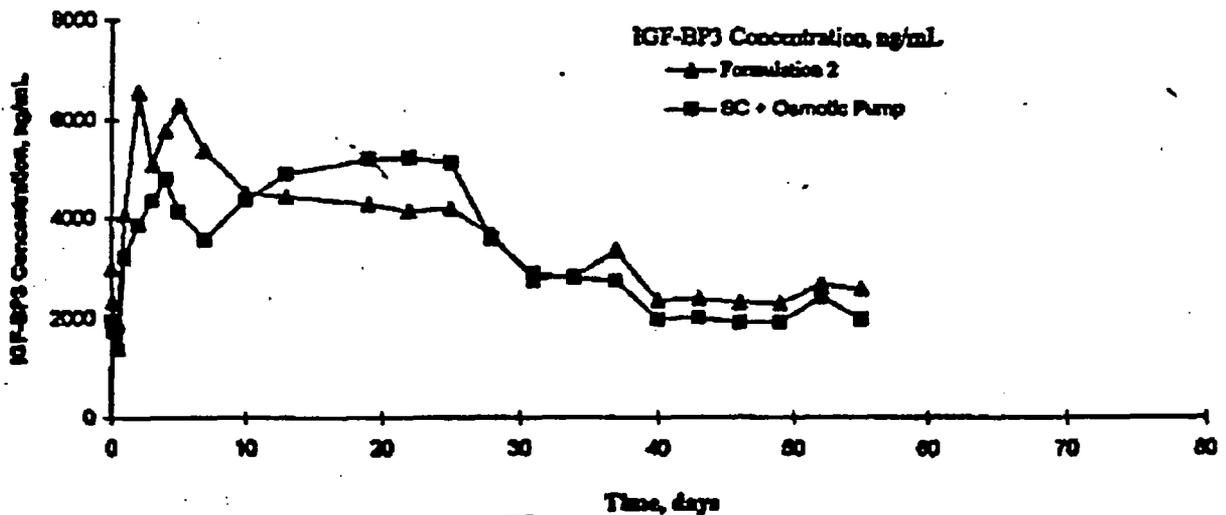
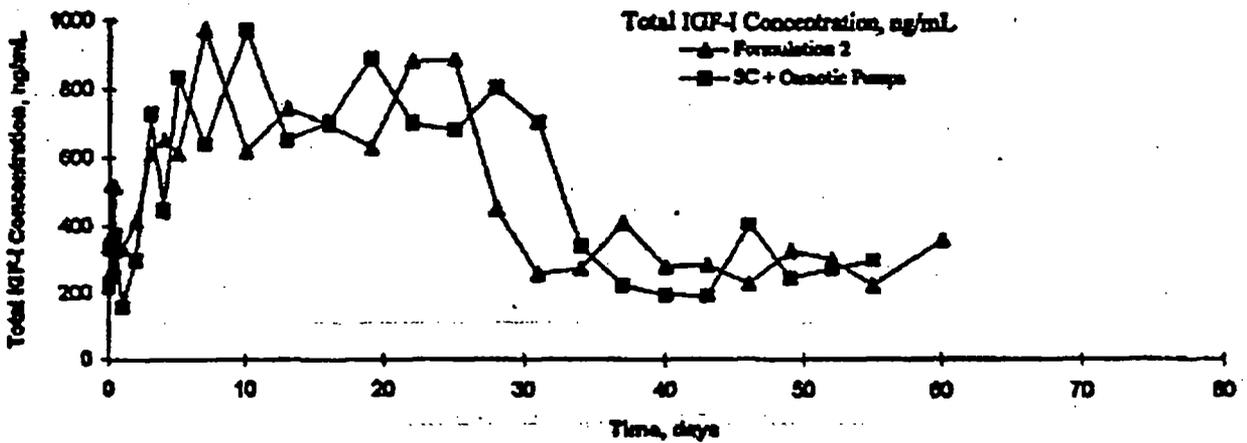
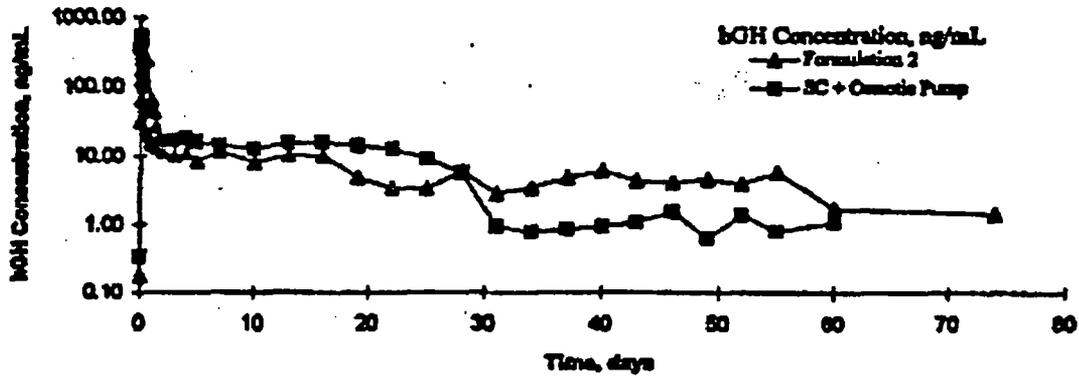
[Sponsor's Vol. 1.5 [redacted] 03-02 (T6) Item 5 p. 35]

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## Correlation of Serum bGH, Total IGF-I, and IGF-BP3 Levels in Rhesus Monkeys:

hGH Formulation 2 and SC + Osmotic Pump



**Summary:**

Three formulations were tested in order to select a formulation for clinical development. The pharmacokinetics and pharmacodynamics of single subcutaneous dose (of each of the three formulations), daily subcutaneous doses for 28 days, and a sustained-release model employing a single s.c. dose and 28 day osmotic pump delivery of hGH were administered to juvenile rhesus monkeys. In general this review concentrated on the selected Formulation 2.

As expected, all [redacted] formulations showed an initial burst of ca 24-36 hours followed by a sustained release phase. [redacted] hGH produced levels of total IGF-1 and IGF-BP3 which were higher than those produced by single or daily injections of hGH. [redacted] hGH serum profiles were more similar to those produced by a s.c. bolus injection followed by an osmotic pump as a sustained-release model.

Although the AUC's<sub>0-last</sub> for Formulation 2 and the single s.c. plus 28 day pump group were similar, the average normalized C<sub>max</sub> of Formulation 2 was less than half that of the single s.c. plus 28 day pump. Injection site enlargements for Formulation 2 monkeys decreased to an unobservable size between days 29 and 35 with only 1 of 4 Formulation sites (ca 4 x 0.1 mm) being identified histologically.

Only one of the Formulation 2 monkeys had quantitatively detectable antibodies (Day 23-end of study). None of the hGH solution monkeys developed detectable antibodies however, they were present in 3 Formulation 1, and 2 formulation 3 monkeys.

**Pharmacokinetic and Pharmacodynamic Study of [redacted] Human Growth Hormone (hGH) PL50 Formulation in Juvenile Rhesus**

**Monkeys:** [redacted]

44805, Study [redacted] 183020. [redacted] -03-04.

Study Initiated 21 Oct 1996. Vol. 1.6 [redacted] 03-04 (T2) Item 5: p. 1.

**Test Article:**

[redacted] hGH Vehicle (Lot J05A6b) containing 5% w/v Dextran 70, 0.1% Tween 20, and 0.9% w/v NaCl in sterile water.

[redacted] hGH test material consisted of 3 different batches of encapsulated drug substance (EDS) as follows:

[redacted] hGH (Lot 0217b): a clinical batch from the small-scale process.

PL50-I (Lot 96-025-63) and PL50-II (Lot 96-025-67) - development batches from the PL50 process (see below).

Each vial of [redacted] hGH contained ca 26 mg of hGH in ca 175 mg of [redacted] hGH (ca 15% hGH load) and was utilized as a single dose unit.

[redacted] hGH PL50, the clinical formulation in use at the time which was manufactured by a small scale (PL-SS) process also included a 15% hGH load in [redacted] microspheres.

[redacted] hGH PL50 formulations (a scale-up process) were compared to [redacted] hGH 217 (a small-scale process) in use at that time.] [redacted] hGH Vehicle (5% w/v Dextran, 0.1% Tween 20 (polyethylenesorbitan monolaurate), in 0.9% w/v Sodium Chloride for Injection, USP was different from the conventional [redacted] hGH Vehicle of the time [3% w/v (carboxymethylcellulose, sodium salt, low viscosity (CMC) [redacted] (0.1% [redacted] w/v Tween 20 (polyethylenesorbitan monolaurate) in 0.9% w/v Sodium Chloride for Injection, USP] for ProLease hGH.]

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NDA 21-075 p. 15

Dose:

[Sponsor's Vol. 1.6 [ ] 03-04 (T2) Item 5 p. 126]

### Summary of PK/PD Study Design in Rhesus Monkeys

Group	Treatment	Dose level (mg/kg)		Dose Regimen	# of Animals
		hGH	ProLease®		
1	[ ] hGH Vehicle	0	0	monthly for 3 months	4
2	[ ] hGH PL50-I	7.5	50	monthly for 3 months	4
3	[ ] hGH PL50-II	7.5	50	single dose	4
4	[ ] hGH 0217	7.5	50	single dose	4

Dose volume was 0.25 mL/kg.

[ ] hGH Vehicle (Group 1) and [ ] hGH PL50-I were administered monthly for 3 months. [ ] hGH PL50-II (Group 3) and [ ] hGH 217 (Group 4) were each administered once on study day 0 to a group of four males by s.c. injection in the shaved upper dorsal region; these animals were returned to the stock colony on study day 56.

Animals:

Juvenile monkeys (4 per group) weighing ca 2.4 to 3.3 kg, were utilized in this study since the endogenous growth hormone level is generally low. All animals were returned to the [ ] stock colony on study day 91.

Results:

Clinical Observations and Survival: All monkeys survived to the end of study and there did not appear to be any treatment-related findings.

Body Weights: Although variable, mean body changes were generally similar for all groups with no apparent trends in mean body or weight gain.

Injection Sites: Sites for hGH vehicle were normal. Sites treated with hGH formulations showed raised areas which ranged up to about [ ] mm x [ ] mm x [ ] mm (length x width x height). These sites showed no signs of inflammation (redness, swelling). No other remarkable changes were seen and raised areas diminished in size as the study progressed.

Hematology: (Post Study)

No remarkable differences reported.

Clinical Chemistry: (Post Study)

No significant differences reported.

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Anti-hGH Antibodies:

[Sponsor's Vol. 1.6] 03-04 (T2) Item 5 p. 130]

### Incidence of Anti-hGH Antibodies in Rhesus Monkeys

Group	Treatment (SC Bolus)	Animals with Anti-hGH Antibody*	Interval with Positive Titer		Maximum Observed Titer
			Monkey	Day	
1	[redacted] hGH Vehicle	0/4	n/a	n/a	n/a
2	[redacted] hGH PL50-I	2/4	892 894	24-91d 38-91d	2.3
3	[redacted] hGH PL50-II	1/4	895	21-56d	1.6
4	[redacted] hGH Lot 0217	0/4	n/a	n/a	n/a

\*At end of the evaluation period.  
n/a: not applicable

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Pharmacokinetics and Pharmacodynamics:Summary of hGH Pharmacokinetic Parameters in Rhesus Monkeys

[Excerpted from Sponsor's Table Vol. 1.6 03-04 (T2) Item 5 p. 129]

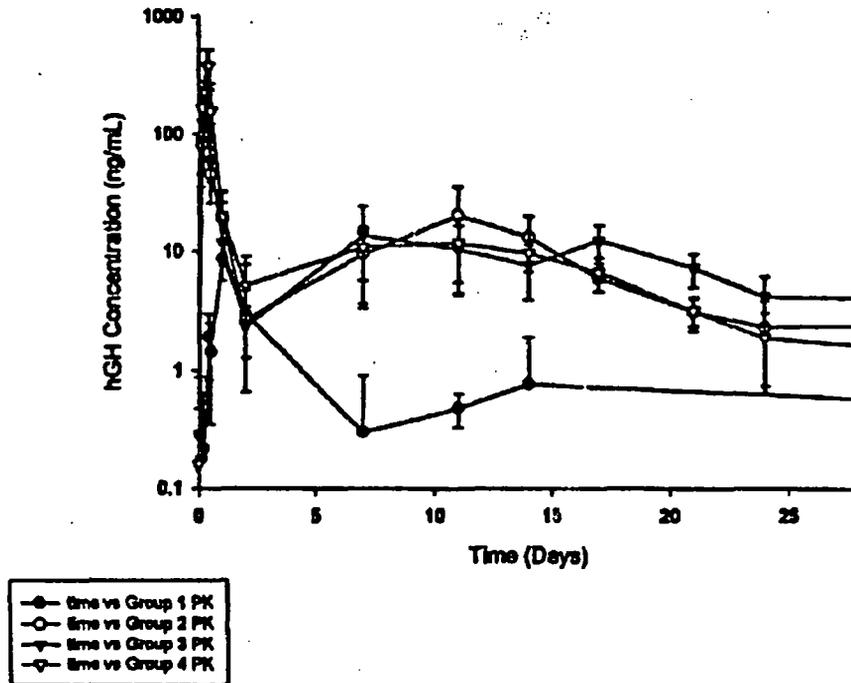
Group 2	Mean	SD
<i>Cycle 1</i>		
$C_{max}$ (ng/mL)	174	68
$T_{max}$ (days)	0.35	0.05
$C_{min(7-14)}$	14.13	7.22
$AUC_{(0-7)}$	74.99	29.39
$AUC_{(7-28)}$	202.22	93.48
$AUC_{(0-28)}$	227.20	122.27
<i>Cycle 2</i>		
$C_{max}$ (ng/mL)	189	85
$T_{max}$	30.78	4.81
$C_{min(15-45)}$	68.72	58.26
$C_{min(45-56)}$	9.31	5.95
$AUC_{(28-30)}$	190.16	77.57
$AUC_{(30-56)}$	1108.83	913.02
$AUC_{(28-56)}$	1298.98	987.06
<i>Cycle 3</i>		
$C_{max}$ (ng/mL)	260	143.16
$T_{max}$	56.48	0.04
$C_{min(63-73)}$	47.96	53.10
$C_{min(77-84)}$	25.59	30.24
$AUC_{(56-58)}$	246.09	138.30
$AUC_{(58-84)}$	994.10	1100.53
$AUC_{(56-84)}$	1240.19	1228.74
<b>Group 3</b>		
$C_{max}$ (ng/mL)	170	58
$T_{max}$ (days)	0.35	0.04
$C_{min(7-14)}$	10.43	6.48
$C_{min(24-36)}$	3.54	2.33
$AUC_{(0-7)}$	74.58	19.60
$AUC_{(7-28)}$	215.72	82.07
$AUC_{(0-28)}$	290.30	99.23
<b>Group 4</b>		
$C_{max}$ (ng/mL)	412	152
$T_{max}$ (days)	0.35	0.05
$C_{min(7-14)}$	10.62	5.47
$C_{min(24-36)}$	1.03	1.00
$AUC_{(0-7)}$	173.56	63.83
$AUC_{(7-28)}$	174.24	60.61
$AUC_{(0-28)}$	347.80	122.40

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All [redacted] formulations exhibited an initial burst of about 24-36 hours followed by a sustained release phase.

### Mean hGH Serum Profiles in Rhesus Monkeys (Cycle 1):

[Sponsor's Vol. 1.6 [redacted]-03-04 (T2) Item 5 p. 132]

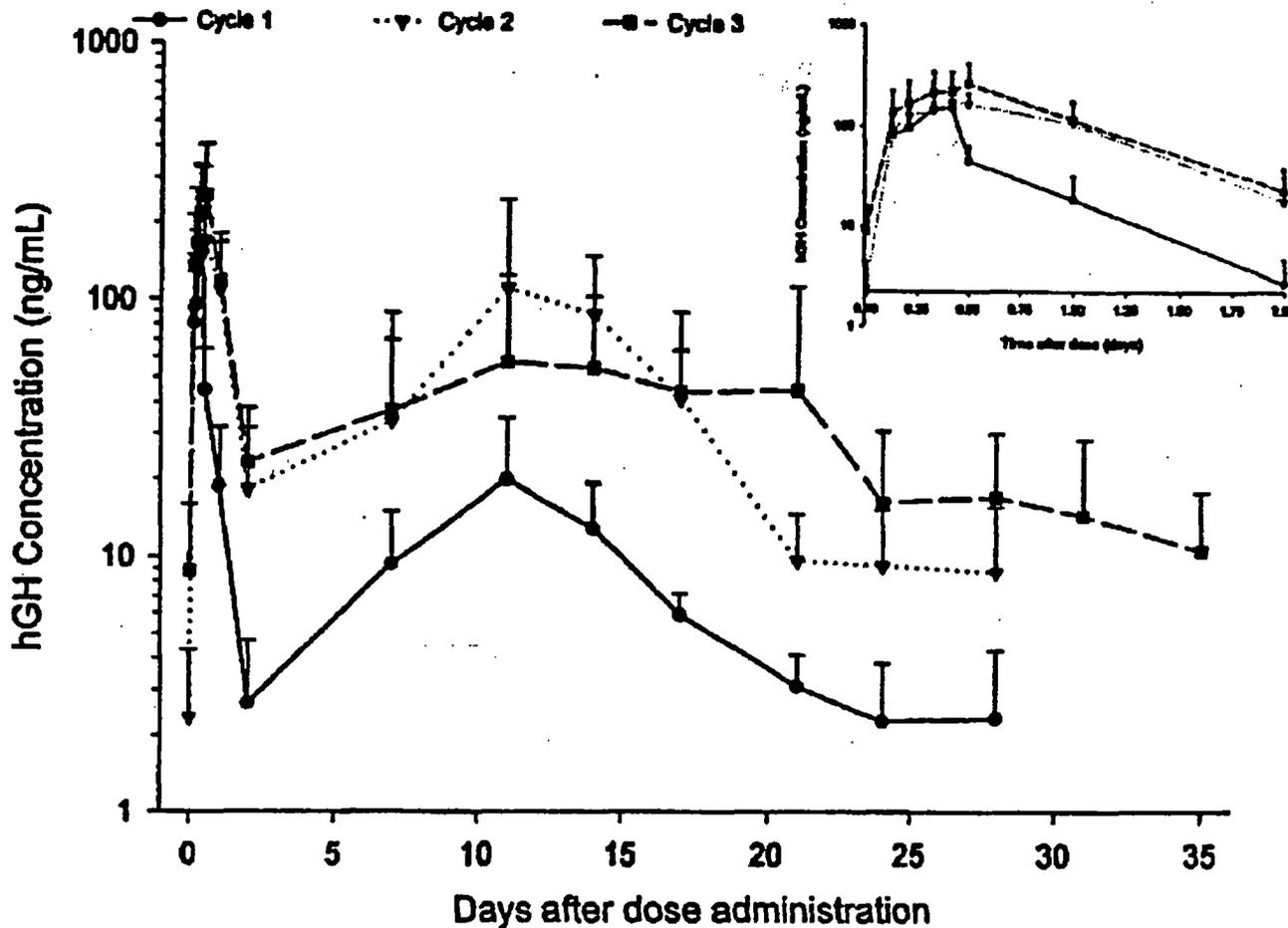


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## Mean hGH Serum Profiles in Rhesus Monkeys Over 3 Consecutive Administration Cycles in Group 2:

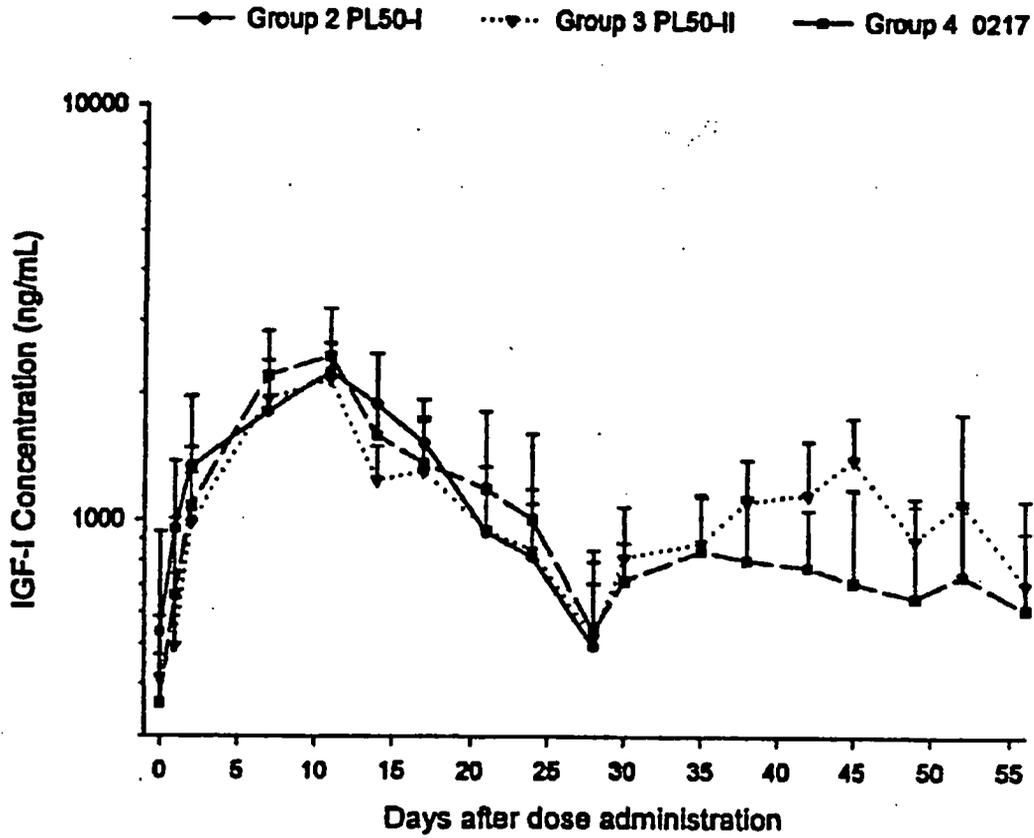
[Sponsor's Vol. 1.6 03-04 (T2) Item 5 p. 133].



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Mean IGF-I Serum Profiles in Rhesus Monkeys:  
[Sponsor's Vol. 1.6]-03-04 (T2) Item 5 p. 134]



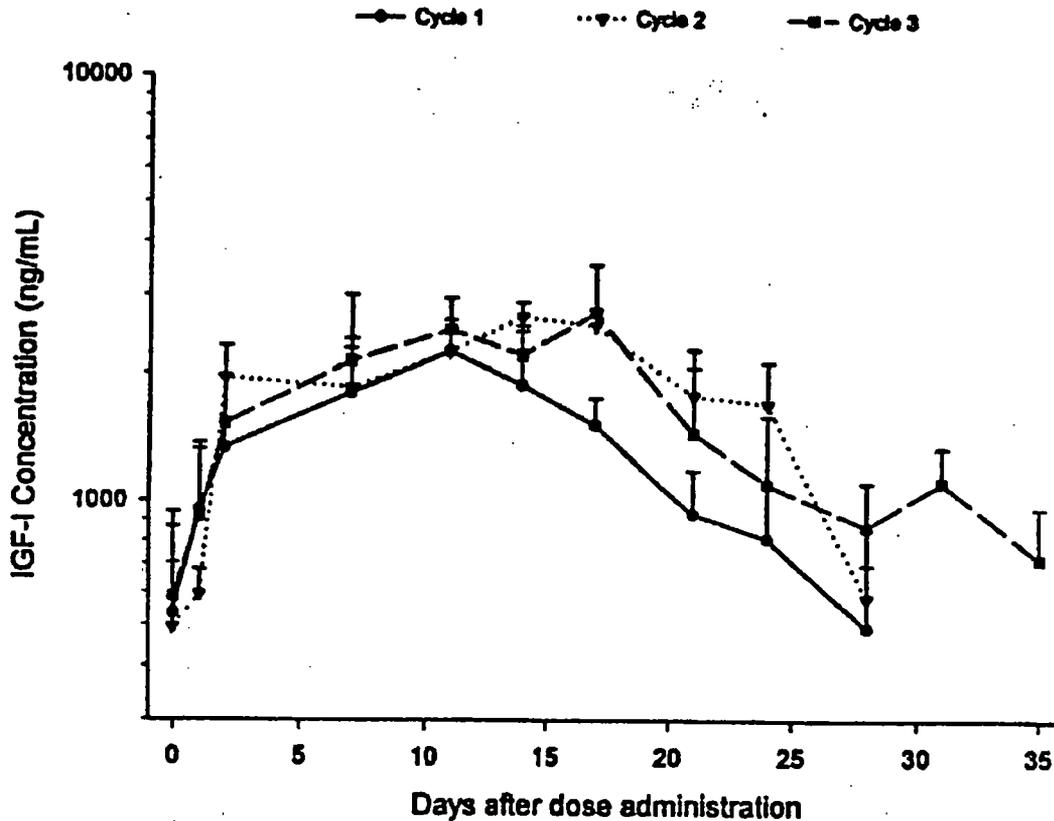
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NDA 21-075 p. 21

## Mean IGF-I Serum Profiles in Rhesus Monkeys Over 3 Consecutive Administration Cycles in Group 2:

[Sponsor's Vol. 1.6-03-04 (T2) Item 5 p. 135]



### Summary:

Little difference was seen when PK and PD of hGH were compared for three groups that received [redacted] hGH. Two batches of [redacted] hGH were prepared by the PL50 process (Groups 2 and 3) and one batch of [redacted] hGH was prepared by the small-scale process (Group 4). Similar patterns of sustained release were noted over the initial 28 day period. There appeared to be little difference in the hGH release profile and resulting production of IGF-I. Group 2 ([redacted] hGH PL50-I), dosed for two additional cycles, showed slightly different release patterns following each administration over the following 28 days. The increase in hGH levels for Group 2 from Cycle 1 to Cycle 3 appeared to have little effect on the resulting IGF-I concentration.

## Pharmacokinetic and Pharmacodynamic Study of [redacted] Human Growth Hormone (hGH) PL500 Formulation in Juvenile Rhesus Monkeys. Vol. 1.4 Tab T3

Conducting Laboratory: [redacted]

Study Number: 0493-54

Study Number: [redacted] 03-05 Final Report dtd 28 April 1998

QA - Present

First Day of Dosing: 20 June 1997

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NDA 21-075 p. 22

Lot Numbers and Batches: [redacted] hGH PL-500-1 (Lot 96-25-102) ([redacted] 483)  
[redacted] hGH PL-500-2 (Lot 96-25-103) ([redacted] 482)  
PL50 (Lot 0410) [redacted] 4810  
[redacted] Vehicle (Lot A01A7a) [redacted] 480  
[3% w/v carboxymethyl cellulose, 0.1% v/v Tween 20 and 0.9% w/v sodium chloride]

Test Material Lot Number	% hGH Load (mg)	% Zinc Load	Copolymer (Source)
PL500 (PL500-1) Lot # 96-25-102	17.5% (30.6)	1.14%	8-10 kD 50:50 PLG Lot # 260188
PL500 (PL500-2) Lot # 96-25-103	17.7% (31.0)	1.17%	8-10 kD 50:50 PLG Lot # 3 7009-327 (ACT II)
PL50 Lot # 0410	15.2% (26.5)	1.01%	8-10 kD Lot # 260188

The control article (diluent, [redacted] vehicle (Lot No. A01A7a), was supplied as a viscous liquid and had the following composition: 3% w/v low viscosity carboxymethylcellulose; 0.1% v/v Tween 20 (polyoxyethylenesorbitan monolaurate); and 0.9% w/v Sodium Chloride for Injection, USP.

[Sponsor's Vol. 1.7 Item 5; [redacted] 03-05 (T1) p. 76]

According to the Sponsor, two batches of [redacted] hGH PL500 were manufactured by a scaled-up (PL-IS) process using a [redacted] hGH PL500 - 1) and an [redacted] Controlled Therapeutics II [redacted]-based polymer [redacted] hGH PL500 - 2). [redacted] hGH PL50, the clinical formulation at the time which was manufactured by a small scale (PL-SS) process, was also included.

## Purpose:

The purpose of this study was to evaluate the pharmacokinetic and pharmacodynamic responses of two different batches of [redacted] hGH PL-500 and one batch of [redacted] hGH PL50 in Rhesus monkeys following either a single subcutaneous or intramuscular administration. In addition the injection sites were assessed for any local tissue effects. The intramuscular route was utilized to assess the performance in case of inadvertent intramuscular administration clinically to man.

## Dosing:

Species/Strain: Male Rhesus Monkeys (*Macaca mulatta*) 2.8 to 3.6 kg; 1.8 to 3.1 years.

[redacted] hGH, suspended in 1.2 ml of [redacted] Vehicle; was administered at a nominal dose of approximately 50 mg [redacted] hGH/kg (~7.5 mg hGH/kg) at a dose volume of 0.34 mL/kg.

Single subcutaneous injections were in the upper dorsal region and intramuscular injections were in the bed of the quadriceps femoris muscle. Monkeys were observed twice daily. In addition they were removed from their cages and the injection sites were examined three times weekly, starting on Day 2.

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[Sponsor's Vol. 1.7 Item 5; 03-05 (T1) p. 12]

**Groups and Dose Levels**

Group No.	Treatment	Dose Route	Number of Males	Nominal Dose hGH (mg/kg)	Nominal Dose hGH (mg/kg)	Dose Volume (mL/kg)
1	Vehicle	SC	4	0 (control)	0	0.34
2	PL500-1*	SC	4	7.5	50	0.34
3	PL500-2*	SC	4	7.5	50	0.34
4	PL50**	SC	4	7.5	50	0.34
5	PL50**	IM	4	7.5	50	0.34

\* PL500 = hGH PL500 formulation; 1 = based polymer; 2 = based polymer  
 \*\*PL50 = hGH PL50 formulation.  
 SC=subcutaneous; IM=intramuscular

**Results:**

**Mortality:** None

**Clinical Signs:** No apparent treatment-related findings.

Dose Site Evaluation showed localized measurable enlargements due to the physical presence of subcutaneous hGH by Day 4. These enlargements decreased in size over time.

**Summary of Injection Site Measurements**

Group	Treatment	Dose Route	Maximum Injection Site Size Range (mm) <sup>1</sup>			Duration of Measurable Size <sup>2</sup> (days)
			Length	Width	Height	
1	vehicle	SC	-	-	-	-
2	PL500-1	SC	26 - 28	18 - 19	8 - 8	8 - 34
3	PL500-2	SC	19 - 26	16 - 19	4 - 9	27 - 46
4	PL50	SC	23 - 31	17 - 23	5 - 11	27 - 34
5	PL50	IM	-	-	-	-

PL500-1 = PL500 based polymer  
 PL500-2 = PL500 based polymer

SC = subcutaneous

IM = intramuscular

- : enlargements not observed, not measured

<sup>1</sup> maximum size range of injections sites from each of four animals within the group

<sup>2</sup> injection sites were measurable until days shown (range of four animals/group); thereafter, the injection sites were too small to measure.

[Sponsor's Vol. 1.7 Item 5; 03-05 (T1) p. 16]

There was no distinct clinical difference among the three hGH formulations. Enlargements subsided to an unmeasurable level by about 1 month in most animals. Subcutaneous injection sites were not observed clinically after Day 46. Microscopically there were some remnants of microspheres still remaining in the subcutaneous injection sites about 2 months later.

**Body Weight:** Weight gain appeared similar across the groups.

**Food Consumption** No apparent treatment-related effect.

**Gross pathology:** Injection site macroscopic observations Days 56 and 57.

Subcutaneous observations showed a thickened area in two monkeys that received [redacted] hGH PL500-1 and a thickened area or a granular foci was noted in 3 monkeys that received hGH PL500-2.

The intramuscular injection site (quadriceps femoris) of one monkey that received [redacted] hGH PL50 showed a thickened area.

Test materials were not seen grossly at any injection site.

**Histopathology of Injection Sites:**

Subcutaneous administration of test drug was associated with chronic inflammation characterized by the presence of macrophages with multinucleate foreign body giant cells and increased thickness of the connective tissue in the subcutaneous compartment. Gross observations were correlated to the microscopic findings. The slight thickening seen grossly at the intramuscular injection site of one monkey, which received [redacted] hGH, proved microscopically to be due to skeletal muscle degeneration.

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**Toxicokinetics:**  
**Pharmacokinetic/Pharmacodynamic Evaluation:**

Summary of Mean Pharmacokinetic Parameters in Rhesus Monkeys (Compiled from various Sponsor's Tables)

Group/ Route	Treatment	Parameter*	HGH Mean ± SD	IGF-1 Baseline Corrected Mean ± SD
1/SC	Vehicle	C <sub>max</sub> , ng/ml	18.5 ± 7.5	918 ± 370
		T <sub>max</sub> , day	11.0 ± 20.7	48 ± 6
		C <sub>avg 2-28d</sub>	3.85 ± 1.07	
		AUC <sub>0-1d</sub>	7.6 ± 4.2	284 ± 327
		AUC <sub>0-2d</sub>	17.1 ± 6.3	689 ± 654
		AUC <sub>0-28d</sub>	117 ± 33	9532 ± 4176
		AUC <sub>0-55/56d</sub>	205 ± 113	24994 ± 14267
2/SC	PL500-1 hGH	C <sub>max</sub> , ng/ml	105 ± 12	1581 ± 503
		T <sub>max</sub> , day	0.37 ± 0.12	15 ± 9
		C <sub>avg 2-28d</sub>	14.6 ± 11.2	
		AUC <sub>0-1d</sub>	70.7 ± 8.3	131 ± 24
		AUC <sub>0-2d</sub>	103 ± 10	411 ± 170
		AUC <sub>0-28d</sub>	469 ± 272	25539 ± 9567
		AUC <sub>0-55/56d</sub>	741 ± 623	37192 ± 15376
3/SC	PL500-2 hGH	C <sub>max</sub> , ng/ml	119 ± 34	1656 ± 314
		T <sub>max</sub> , day	0.42 ± 0.07	15 ± 5
		C <sub>avg 2-28d</sub>	12.3 ± 6.8	
		AUC <sub>0-1d</sub>	74.3 ± 12.1	319 ± 322
		AUC <sub>0-2d</sub>	98 ± 9	892 ± 630
		AUC <sub>0-28d</sub>	405 ± 193	29908 ± 9177
		AUC <sub>0-55/56d</sub>	718 ± 400	42706 ± 15676
4/SC	PL50 hGH	C <sub>max</sub> , ng/ml	197 ± 38	1540 ± 491
		T <sub>max</sub> , day	0.35 ± 0.10	14 ± 0
		C <sub>avg 2-28d</sub>	4.42 ± 0.75	
		AUC <sub>0-1d</sub>	121 ± 30	313 ± 50
		AUC <sub>0-2d</sub>	180 ± 91	805 ± 204
		AUC <sub>0-28d</sub>	316 ± 125	25463 ± 5120
		AUC <sub>0-55/56d</sub>	395 ± 139	35169 ± 8779
5/IM	PL50 hGH	C <sub>max</sub> , ng/ml	373 ± 75	1128 ± 521
		T <sub>max</sub> , day	0.27 ± 0.13	8 ± 2
		C <sub>avg 2-28d</sub>	9.5 ± 1.1	
		AUC <sub>0-1d</sub>	176 ± 25	185 ± 138
		AUC <sub>0-2d</sub>	211 ± 25	463 ± 211
		AUC <sub>0-28d</sub>	431 ± 51	15331 ± 7300
		AUC <sub>0-55/56d</sub>	557 ± 133	23145 ± 12227

\* Units - C<sub>avg</sub>, ng/mL; AUC, ng•d/mL

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NDA 21-075 p. 26

Based on AUCs the two processes appeared similar. The  $C_{max}$  values for the two PL500 batches using scale up of [redacted] hGH from two different sources were similar,  $105 \pm 12$  and  $119 \pm 34$  ng/mL while that of PL50 was considerably higher i.e.  $197 \pm 38$  ng/ml. Following IM dosing (PL50) the increase in  $C_{max}$  was  $373 \pm 75$  ng/mL which was significantly greater than the other treatments.

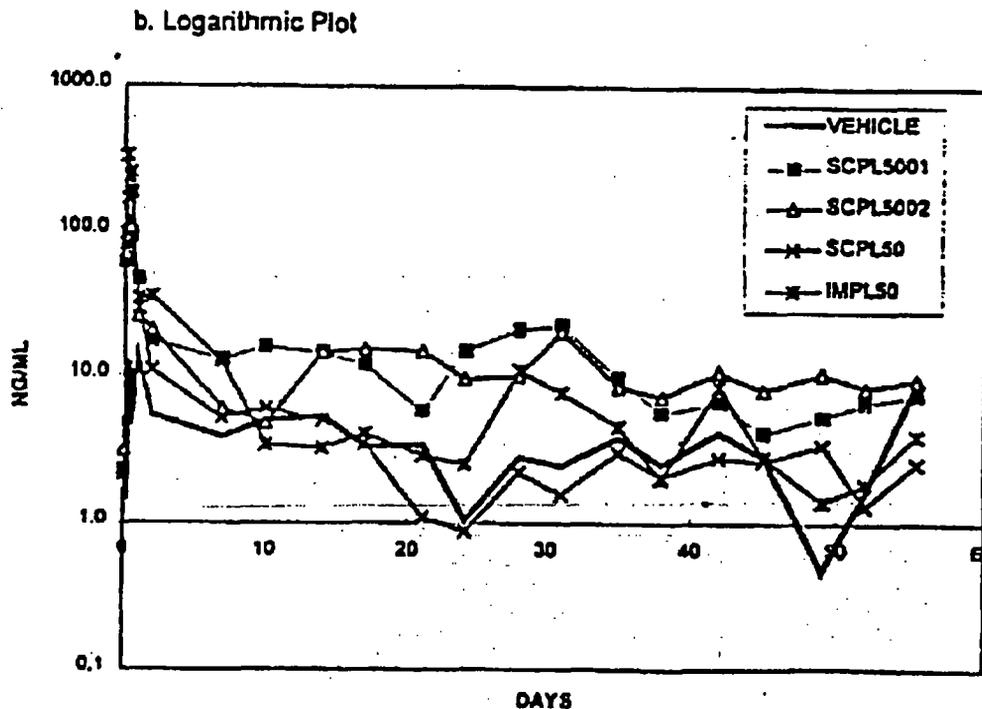
When the sustained release portion of the hGH curves (day 2-28 ) were compared the difference between Groups 4 and 5 showed a significant difference.  $C_{avg}$  for Groups 2,3,4 and 5 were  $14.6 \pm 11.2$ ,  $12.3 \pm 6.8$ ,  $4.42 \pm 0.75$ , and  $9.5 \pm 1.1$  ng/mL, respectively.

**Antibody Titer:** The only positive titers were as follows:

Anti-hGH developed in 3/16 (19%) monkeys that received hGH. This value is reported to be similar to that previously seen in monkeys. One Group 2 [redacted] hGH PL500-1 monkey had a log titer of 1.86 on day 29 with seroconversion occurring on day 22. Two Group 3 [redacted] hGH PL500-2 monkeys had titers of 1.77 and 1.38 with seroconversion on days 18 and 29, respectively.

## Mean Serum hGH Concentrations in Rhesus Monkeys (Day 0 – Day 55/56)

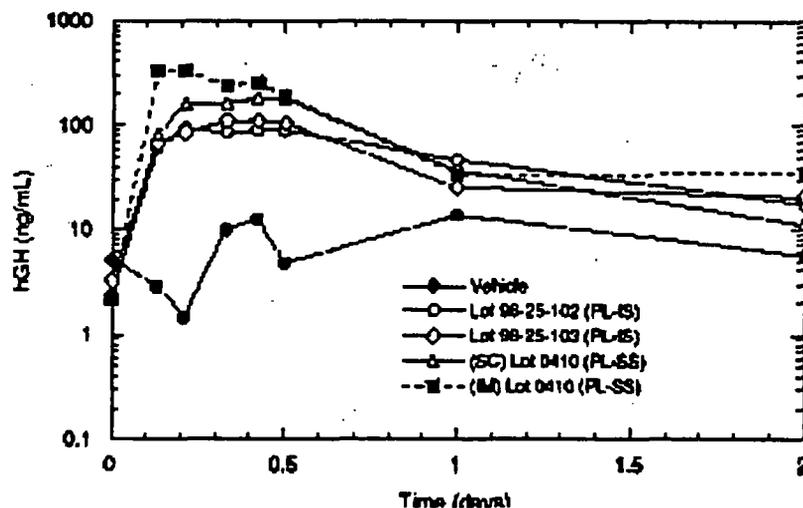
[Sponsor's Vol. 1.7 Item 5; [redacted] 03-05 (T1) p. 90]



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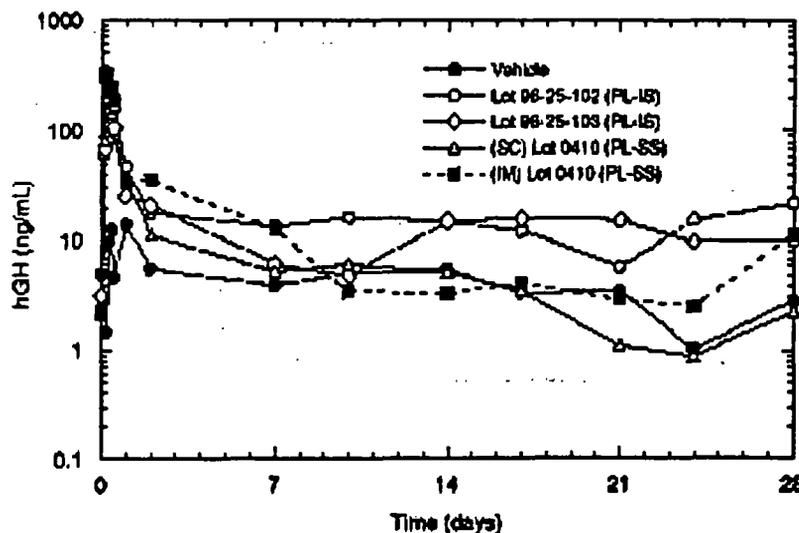
[Sponsor's Vol. 1.5, (T4) Item 5, p. 128]

## Mean hGH Profiles for the Initial Release Phase (Days 0-2) in Rhesus Monkeys for Small Scale (PL-SS) and Intermediate Scale (PL-IS) Materials (Study 03-05)



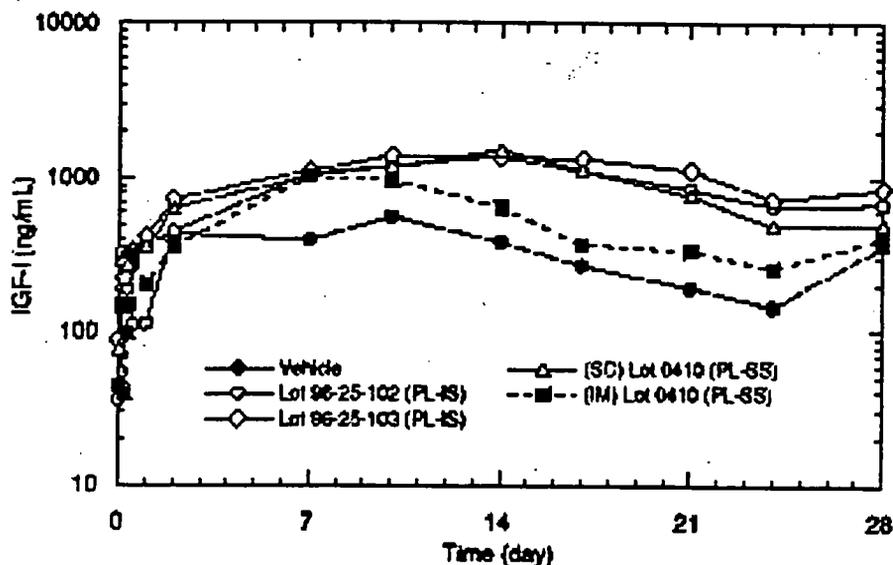
[Sponsor's Vol. 1.5, (T4) Item 5, p. 129]

## Mean hGH Profiles for the Sustained Release Phase (Days 2-28) in Rhesus Monkeys for Small Scale (PL-SS) and Intermediate Scale (PL-IS) Materials (Study 03-05)



[Sponsor's Vol. 1.5, (T4) Item 5, p. 131]

## Mean Baseline-Corrected Serum IGF-I Profiles in Rhesus Monkeys for Small Scale (PL-SS) and Intermediate Scale (PL-IS) Materials (Study [redacted] 03-05)



### Summary of In Vivo Evaluations of Selected [redacted] hGH (Nutropin Depot) Lots of Differing Process Scale Manufacture in the Rat: [redacted] Product Development

Report PD-03-011 dtd 10 Feb 99.

[Vol. 1.7 (T3) PD-03-011 Item 5, p. 1,7]

For each lot of Nutropin Depot used in clinical trials, the pharmacokinetic profiles in the rat were compared to assess the similarities of each lot in an in vivo model. [The main purpose of this report is to compile relevant rat serum hGH concentration data generated during the development of Nutropin Depot into a single source document. In addition, the effect of production scale on the initial rhGH release phase was investigated.]

#### Scale Designations:

Clinical Scale: Lots of several grams sizes:  
(Phase I [redacted] 03-001 and Phase I/II: [redacted] 03-002)

Small Scale: [redacted] PL-SS

Intermediate Scale: [redacted] PL-IS  
(Phase I/II and Phase III human efficacy studies)

#### Materials and Methods:

##### Test Animals:

Male Sprague-Dawley Rats weighing 403 to 611 gms. Study hGH05 and hGH08 were not immunosuppressed; all other animals (CS/HC) were immunosuppressed. [Apparent serum concentrations of hGH in rats in the nonimmunosuppressed studies (hGH-05 and -08) began to rise after about a week presumably, according to the sponsor, because of induction of rat anti-hGH antibody. This prompted the use of the immunosuppressed regimen for further studies.

Route of Injection: Subcutaneous (s.c.) injection into the mid-scapular region.

Injection vehicle: In an early study (hGH 53-A), microspheres were suspended in a dextran vehicle (dextran 70, 0.9% NaCl, 0.1% Tween 20). All other study vehicles consisted of carboxymethylcellulose (3% CMC low viscosity, 0.1% Tween 20 (polysorbate 20), 0.9% NaCl).

Doses: Nominal doses contained 50 mg of microspheres containing 7.5 mg of rhGH (= 10 mg hGH/mL). Approximately 0.75 mL was administered to each rat.

**Summary of In Vivo Evaluations of Selected [redacted] hGH (Nutropin Depot) Lots of Differing Process Scale Manufacture in the Rat.**

[Sponsor's Vol. 1.7 PD-03-011 (T3) Item 5 p. 2]

Process Scale	Lots (N)	C <sub>max</sub>	Dose Normalized C <sub>max</sub>	AUC <sub>0-2</sub>	AUC <sub>0-∞</sub>	AUC <sub>0-2</sub> % of Total
Clinical Scale	7	987 ± 502	888 ± 437	467 ± 238	743 ± 239	65.2 ± 16.1
Small Scale	8	984 ± 519	889 ± 583	395 ± 170	444 ± 150	81.5 ± 15.7
Intermediate Scale	6	683 ± 273	637 ± 223	261 ± 146	423 ± 137	78.2 ± 10.3

**Summary:**

HGH release in vivo is characterized by an initial burst phase followed by a period of sustained release. C<sub>max</sub> values used in clinical trials were similar to the range of C<sub>max</sub> values seen with Small scale materials. There appeared to be little change in the initial release presentation during the manufacturing scale up process. There is an apparent decrease in C<sub>max</sub> for the Intermediate scale compared to the clinical scale lots, however, the percent burst i.e. percent AUC<sub>0-2</sub> was similar for the Small and Intermediate Scale lots.

**Nutropin Depot Nonclinical ADME Species Comparisons: Pharmacokinetics, In Vitro/In Vivo Correlation's and Safety Factors:** Genentech Report 99-046-0750 dtd 3/26/99.

[Vol. 1.7 (T4) 99-046-0750 Item 5, p. 1] Nutropin Depot Lot 0217 only.

This report documents species comparison. Analyses included:

- 1) comparisons of the subcutaneous (SC) pharmacokinetics (PK) in rats, monkeys and humans for Nutropin Depot, Nutropin and Nutropin AQ;
- 2) correlation's of in vitro hGH release from Nutropin Depot and in vivo serum profiles in rats; and
- 3) calculations of safety factors from the Nutropin Depot toxicokinetic study (AT-03-05).

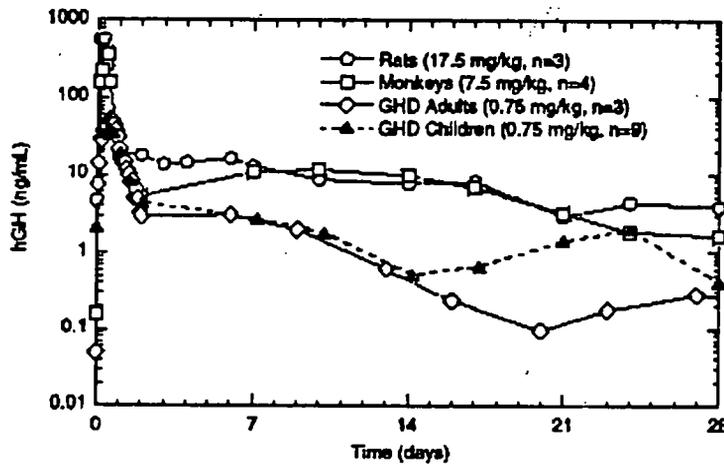
Rats (17.5 mg/kg, n = 3)  
 Monkeys (7.5 mg/kg, n = 4)  
 GHD Adults (0.75 mg/kg, n = 3)  
 GHD Children (0.75 mg/kg, n = 9)

Study hGH25A  
 Study [redacted]-03-04  
 Study [redacted]-03-001  
 Study [redacted]-03-002

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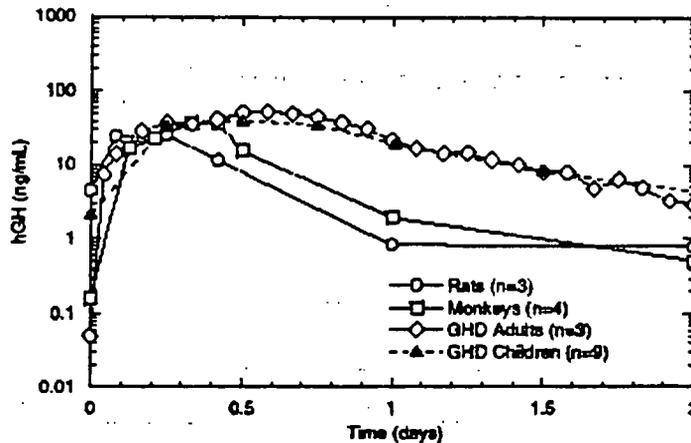
## Serum Concentration-Time Profiles (Days 0-28) for Rats, Monkeys and Humans Following single Administration of Nutropin Depot (Lot 0217, PL-CS)

[Sponsor's Vol. 1.7 (T4) 99-046-0750 Item 5: p. 1]



## Dose-normalized Serum Concentration-Time Profiles (Days 0-2) for Rats, Monkeys and Humans Following Single Administration of Nutropin Depot (Lot 0217, PL-CS). Data normalized to a 0.75 mg/kg dose.

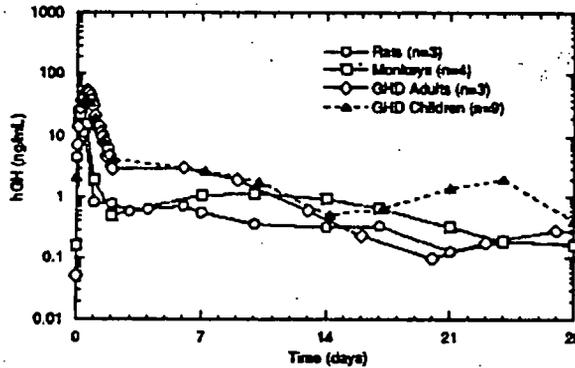
[Sponsor's Vol. 1.7 (4) 99-046-0750 Item 5 p. 6]



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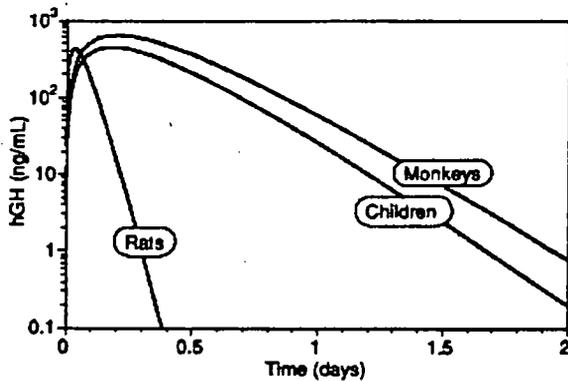
**Dose-normalized Serum Concentration-Time Profiles (Days 0-28) for Rats, Monkeys and Humans Following Single Administration of Nutropin Depot (Lot 0217, PL-CS). Data normalized to a 0.75 mg/kg dose.**

[Sponsor's Vol. 1.7 (4) 99-046-0750 Item 5 p. 5]



**Simulated Serum hGH Concentration-Time Profiles for Single SC Bolus Doses of Solution rhGH at a Dose of 0.75 mg/kg in Rats, Monkeys and Children**

[Sponsor's Vol. 1.7 99-046-0750 (T4) p. 7]



**Summary:**

Serum hGH concentration time profiles showed expected initial and sustained release phases in rats, monkeys and humans. All species showed rapid initial absorption of released rhGH. Rats and monkeys were the first to reach maximum ( $C_{max}$ ) concentrations which were also higher in these species as reflected primarily due to higher dose levels in these species. After the initial burst hGH profiles became more similar in shape and terminal slope for about two weeks for all three species. [This is reported to be in contrast to the species-specific SC disposition profiles seen with rhGH solution.]

[It was shown in vitro that the initial 24-hour period represents rhGH released by diffusion from the microsphere surfaces and by initial hydration of the microspheres.]

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TOXICOLOGY

[redacted] hGH

**Study Title:** Three-Month [Toxicokinetic] Study with [redacted] Human Growth Hormone in Rhesus Monkeys

**Study No:** AT-03-05 [redacted] 6403-108

Original NDA 21,075 Vol 1.2, page 1 Tab (T1) [Final Report]

**Conducting laboratory and location:** [redacted]

**Date of study initiation:** 18 Aug 1995

**GLP compliance:** Yes

**QA- Report** Yes (X) No ( ) The final report prepared by [redacted] and the pathology report prepared by [redacted] have been reviewed by [redacted]. The PK and PD portions of the study were conducted at [redacted] and audited by their Q.A.

**Methods:** Animals in Groups 1, 3, and 4 received a single s.c. injection into the dorsal cervical region on Day 1. Animals in Groups 5, 7, and 8 received a single subcutaneous injection into individual sites (Injection Sites 1, 2, and 3) in the dorsal cervical region on Days 1, 29, and 57. Three animals in Group 8 were observed for an additional 7 weeks after Day 92. Monkeys in group 2 received three s.c. injections into the dorsal cervical region for 4 weeks. Monkeys in Group 6 received 3 s.c. injections/week into the dorsal cervical region for 12 weeks.

**Dosing:**

- species/strain: Male rhesus monkeys (Macaca mulatta)
- #/sex/group or time point:

[Sponsor's Vol.1.2 AT-03-05 (T1) Item 5, p. 15]

Group	Duration	Treatment <sup>a</sup>	Dose Level <sup>b</sup> (mg hGH/ kg/dose)	Dose Concentration (mg hGH/mL)	Dose Volume (mL/kg/dose)	Number of Males
1	1-month	[redacted] Vehicle	0	0	0.33	4
2	1-month	[redacted] hGH	0.627	5.1	0.123	4
3	1-month	[redacted] hGH	1.5	4.5	0.33	4
4	1-month	[redacted] hGH	7.5	22.73	0.33	4
5	3-months	[redacted] Vehicle	0	0	0.33	4
6	3-months	[redacted] hGH	0.627	5.1	0.123	4
7	3-months	[redacted] hGH	1.5	4.5	0.33	4
8 <sup>c</sup>	3-months	[redacted] hGH	7.5	22.73	0.33	7

a Groups 1, 3, and 4 received a single subcutaneous injection on Day 1. Groups 5, 7, and 8 received a single subcutaneous injection on Days 1, 29, and 57. Group 2 received three subcutaneous injections/week for 4 weeks. Group 6 received three subcutaneous injections/week for 12 weeks. Multiple injections were given at different sites in the same general region. Each injection site of the animals in Groups 1, 3, 4, 5, 7, and 8 was separately marked and identified for examination. [redacted] human growth hormone is designated as [redacted] hGH and human growth hormone is designated as hGH.

b Nominal levels.

c After Day 92, three animals in Group 8 continued on recovery for 7 additional weeks.

- age: 11-17 months 1 animal ca 24 months
- weight: 1.9 to 3.2 kg
- satellite groups used for toxicokinetics or recovery: See Group 8.

**Drug, lot:**

[redacted] hGH Lot 0081a supplied as 7.5 mg hGH in 50 mg [redacted] microspheres  
 [redacted] hGH Lot 0081c supplied as 30 mg in 200 mg [redacted] microspheres  
 Control - hGH Lot 95-029-169 supplied as a 5.1 mg/ml solution.

Vehicle Lot 0111 [3% w/v carboxymethylcellulose, sodium salt, low viscosity  
 The hGH lot used in the study was analytically determined to contain a load of  
 16.6% hGH.

**Formulation/vehicle:** The test-material used in this study was an PLG Copolymer (with hydrophilic end groups) microsphere formulation with a 15% hGH load (16.6% analytical), selected for development in a previous study in rhesus monkeys 3-02).

**Observations and times:**

**Clinical signs:** [Twice daily for mortality and moribundity and once daily for poor health or abnormal behavior. Animals were also observed within 5 min of injection for abnormal clinical signs. Injection sites were examined 3x/wk.]

- **Body weights:** [weekly]
- **Food consumption:** [Daily]
- **Clinical chemistry:** [Before Treatment Day -13; Groups 1,2,3,4 also Days 3 and 29; Groups 5, 6, 7,8 also Days 15,29,43,57,71, 92.; Group 8 recovery also Days 113 and 141.]
- **Urinalysis:** [At necropsy on Days 29 and 92]
- **Organ weights:** [See chart.]
- **Gross pathology:** At necropsy (Days 29 and 92).
- **Histopathology:** [See Chart.] Tissues from recovery animals were not examined microscopically because there were no test material-related significant lesions seen at the Day 92 sacrifice.
- **Toxicokinetics:** [Bioanalytical Blood Collection: 2 blood samples at time of necropsy from Group 3 animals sacrificed Day 26 (unscheduled).
- **Scheduled Blood Collections:** (See below.)

On Day 1, samples were collected from animals in Groups 1, 3, and 4 before dosing and at approximately 0.5, 3, 5, 8, 10, 12, and 14 hours postdose. Samples were also collected on Days 2, 3, 8, 12, 15, 18, 22, and 25 (Protocol Deviations for exceptions) at approximately the same time each day ( $\pm 1$  hour). Samples were also collected on Day 29 before the scheduled necropsy.

Beginning on Day 1, samples were collected from animals in Group 2 before dosing and at approximately 0.5, 1, 2, 3, 5, and 24 hours postdose. Samples were also collected on Days 8, 15, and 22 before dosing and at approximately 1 hour postdose. One sample was collected on Day 29 before the scheduled necropsy.

On Days 1, 29, and 57, samples were collected from animals in Groups 5, 7, and 8 before dosing and at approximately 8, 10, 12, and 14 hours postdose. Additional samples were collected on Days 5, 10, 15, 20, 25, 34, 39, 44, 49, 54, 62, 67, 72, 77, 82, and 87 at approximately the same time each day ( $\pm 1$  hour). One sample was collected on Day 92 before the scheduled necropsy and from the recovery animals. In addition, samples were collected from Group 8 recovery animals on Days 93, 96, 100, 103, 107, 110, 114, 117, 121, 124, 128, 131, 135, 138, and 141 at approximately the same time each day ( $\pm 1$  hour).

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Also on Days 1, 29, and 57, samples were collected from animals in Group 6 before dosing and at approximately 0.5, 1, 2, 3, and 5 hours postdose. Additional samples were collected on Days 8, 15, 22, 36, 43, 50, 64, 71, and 78 before dosing and at approximately 1 hour postdose, and one sample was collected on Days 85 and 92. \_

- **Other:** All animals were screened for endogenous growth hormone levels determined from serum samples collected during Weeks -5 and -3. Baseline samples collected Days -7, -5 and -3 for GH levels.

**Results:**

- **Mortality:** Day 26 – 1 monkey given [redacted] hGH at 1.5 mg hGH/kg (No. 103553, Gp 3) was sacrificed due to poor health (sponsor considered this secondary to anorexia and prolonged diarrhea and not related to test material). This monkey had moderate hypoproteinemia and hypoalbuminemia (5.4 and 2.5 g/dL, respectively) and severe hyponatremia and hypochloridemia (124 and 92 mmol/L, respectively). Histopathological diagnosis = enterocolitis.

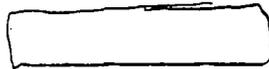
- **Clinical signs:** No reported test material related findings.

**Injection Site –**

Administration of [redacted] hGH reported to have produced nonirritating local masses (enlargements) at the subcutaneous injection site that subsequently regressed over the course of the study. In general the onset of enlargements was earlier and generally larger for Groups 4 and 8 (7.5 mg/kg). No clinical signs of irritation or discomfort were noted at any of the [redacted] hGH injection sites.

[Sponsor's Vol.1.2 AT-03-05 (T1) Item 5, p. 55]

**Summary of Injection Site Observations**



DAYS 2-141	NUMBER OF ANIMALS AFFECTED						
	SEX:	MALE			FEMALE		
CATEGORY	GROUP:	1	2	4	5	7	8
KEYWORD	DOSE:	0	1.5	7.5	0	1.5	7.5
QUALIFIER	UNITE:	MG/K	MG/K	MG/K	MG/K	MG/K	MG/K
	NUMBER:	4	6	4	4	4	7
<b>INJECTION SITE 01</b>							
REDNESS		4	4	4	4	4	7
SWELLING		4	4	4	4	4	7
MASS		0	3	4	0	3	7
<b>INJECTION SITE 02</b>							
REDNESS		-	-	-	4	4	7
SWELLING		-	-	-	4	4	7
MASS		-	-	-	0	3	7
<b>INJECTION SITE 03</b>							
REDNESS		-	-	-	4	4	7
SWELLING		-	-	-	4	4	7
MASS		-	-	-	0	4	7

- **Body weights:** Animals generally gained weight during the study. No statistically significant test material-related changes in body weights or cumulative body weight gains were reported.
- **Food consumption:** Although there were several observations of low food consumption, they did not appear to be treatment material-related.
- **Hematology:** No apparent treatment-related findings.  
Group 8 had significantly higher Hb on Day 57 and at Day 92 significantly lower platelet counts.
- **Clinical chemistry:**  
Groups 1 - 4, Days 3 and 29:— No statistically significant differences between groups that were not present Day -13. (See attached review dtd. 3 Jul 96).  
Groups 5 - 8, Days 15, 29, 43, 57, 71 and 92. No apparent differences between groups considered to be effects of hGH or [ ] hGH. No significant differences between groups were seen on Days 15, 29 or 71 and there were very few significant differences at other intervals. Group 8 had significantly lower chloride on day 43 compared to Group 6. Compared to Group 7, significantly higher albumin, and significantly higher gamma-glutamyl transferase. Group 7 had significantly lower gamma-glutamyl transferase than Group 5 at Day 92. The sponsor considered these differences to be incidental and unrelated to test material.  
Group 8 - Recovery animals. Days 113 and 141 - Clinical pathology was unremarkable.
- **Urinalysis** No apparent test material-related effects.
- **Organ Weights**  
Day 29 Interim Sacrifice: No statistically significant differences in absolute or relative organ weights.  
Day 92 Terminal Sacrifice: Brain - the absolute weight was significantly increased in high dose [ ] hGH compared with that in low dose males. However, there was a lack of a significant difference from that of the control group and an absence of a significant change in the brain-to-body weight percentage.  
Day 141 Recovery Sacrifice: Only 3 animals at sacrifice - no statistical evaluation of data.
- **Gross pathology**  
Day 29 Interim Sacrifice: Injection sites of all animals given 7.5 mg/kg hGH/kg [ ] showed light-colored foci and/or red foci within the subcutaneous injection site tissue. One 1.5 mg/kg hGH/kg [ ] had red foci within injection site subcutaneous tissue.  
Day 92 Terminal Sacrifice: 2/4 [ ] hGH 7.5 mg hGH/kg animals showed red areas at injection site 2. 3 of 4 animals each showed red areas at injection sites of 1.5 and 7.5 mg hGH/kg [ ] site 3.  
Day 141 Recovery Sacrifice: No macroscopic findings.
- **Histopathology**  
Day 29 Interim Sacrifice: Examination of all tissues except injection sites showed no apparent drug-related histopathologic findings. However, subcutaneous injection sites of two 0.627 mg hGH/kg animals showed minimal or slight lymphohistiocytic infiltration in the subcutis; one had minimal hemorrhage and fibrosis.  
Day 92 Terminal Sacrifice:  
No microscopic findings were associated with test material administration. One hGH animal had a minimal lymphohistiocytic infiltrate in the superficial dermis.  
Day 141 Recovery Sacrifice: No evaluation since no significant findings were seen in [ ] animals at 92 Day Sacrifice.

**Unscheduled Death:** 1 monkey sacrificed Day 26 due to poor health. Thymus was small and microscopically moderately involuted. Several sections of the intestine showed minimal to slight subacute inflammation that the sponsor indicates may have contributed to the debilitated status through protein, fluid, and electrolyte loss.

**Toxicokinetics:** See Below.

**Key Study Findings:**

The inflammatory processes found in injection sites of monkeys of the 3-month sacrifice were in general qualitatively similar to those seen at the one-month sacrifice. Microspheres were phagocytized by macrophages and foreign body giant cells. The microspheres were in an advanced stage of intracytoplasmic disintegration in the three month sacrifice animals than in those from the 1-month sacrifice. The 3-month sacrifice showed no evidence that the test material was directly cytotoxic to the macrophages or other cells in these tissues.

When present at the 3-month sacrifice, fibrosis occurred at a higher incidence in Group 8 (not recovery) than in Group 7. Recovery Group 8 animals showed inflammation and fibrosis to be recovered or in the process of recovery. Although there was a higher incidence of lymphocytes and plasma cells present at injection sites of Group 8, none of the injection sites from the Group 8 recovery sacrifice had lymphoplasmacytic infiltration. Severity of the inflammation of the injection sites of the high dose [redacted] hGH Groups (4 and 8) evaluated ca 1-month after s.c. administration ranged from mild (+2) to moderate (+3).

**Overall Toxicology Summary:**

A local tissue reaction consisting primarily of chronic inflammation and fine diffuse interstitial fibrosis followed subcutaneous administration of [redacted] hGH to rhesus monkeys. The mass of [redacted] hGH remained localized at the injection sites and diminished over time; the intensity of the local tissue reaction and the persistence of microsphere material being drug-related. High dose animals showed residual polymer up to 112 days after injection. However, by 140 days after administration, the microspheres and the local inflammatory response had resolved. Microsphere absorption and resolution of local inflammation was complete by 91 days after administration of low dose [redacted] hGH. No biologically significant difference in local tissue reaction of microsphere degradation was seen following single or multiple [redacted] hGH dosing. The test material was absorbed from the injection sites and [redacted] hGH was not cytotoxic. Examination of tissues other than injection sites showed no apparent drug-related histopathologic findings.

**Toxicokinetic Parameters:**

Comparisons were made between [redacted] hGH 1.5 and 7.5 mg/kg and hGH solution, 0.627 mg/kg in a toxicology/pharmacokinetics study in rhesus monkeys (4 per group - 3 additional in Group 8 for recovery).

[redacted] hGH produced a sustained hGH release and elevated IGF-I levels at both of the doses evaluated. hGH release ranged from 1 to 3 days for the low dose and 17 to 19 days for the high dose while that for IGF-I levels for the low and high doses ranged from ca 1 to 7 days and 20 to 25 days, respectively. The pharmacokinetic disposition of hGH appeared to be independent of dose.

There did not appear to be any AUC or  $C_{avg}$  effects that would suggest accumulation in absorption, distribution or elimination of hGH over the 90 day period. There was a significant  $C_{max}$  change between Month 1 and Month 2 only. It was not apparent why  $C_{max}$  increased following the second and 3<sup>rd</sup> month injections.

Three monkeys showed anti-hGH antibodies - one receiving hGH and two that received high dose [redacted] hGH.

## Three-Month Pharmacokinetic Parameters of hGH in Rhesus Monkeys:

hGH vs. hGH Solution

	GROUP 6 (hGH Solution) <sup>4</sup>						GROUP 7 (hGH, Low Dose)						GROUP 8 (hGH, High Dose)					
	Month 1		Month 2		Month 3		Month 1		Month 2		Month 3		Month 1		Month 2		Month 3	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Dose Level, mg/kg	0.63	0.00	0.63	0.00	0.63	0.00	1.50	0.00	1.50	0.00	1.50	0.00	7.50	0.00	7.50	0.00	7.50	0.00
Body Weight <sup>1</sup> , kg	2.50	0.34	2.65	0.38	2.73	0.39	2.98	0.29	2.43	0.34	2.43	0.39	2.98	0.42	2.60	0.48	2.69	0.37
Dose <sup>2</sup> , mg	1.57	0.21	1.66	0.24	1.71	0.34	3.96	0.43	3.53	0.71	3.64	0.58	18.99	3.62	19.50	3.57	20.14	2.75
AUC <sub>0-24</sub> <sup>3</sup> , ng·day/mL	82	25	73	11	75	21	134	27	229	28	242	143	647	209	1032	491	1114	492
AUC <sub>0-24</sub> <sup>3</sup> , ng·day/mL	NA	NA	NA	NA	NA	NA	89	24	211	5	177	56	347	71	991	247	711	414
C <sub>max</sub> , ng/mL	628	196	569	136	526	192	95	16	180	19	175	44	282	52	280	96	337	156
T <sub>max</sub> , day	0.04	0.03	0.03	0.04	0.06	0.03	0.00	0.04	0.31	0.05	0.35	0.04	0.05	0.11	0.03	0.07	0.08	0.06
C <sub>avg</sub> <sup>3</sup> , ng/mL	NA	NA	NA	NA	NA	NA	2.55	2.28	2.32	1.79	3.74	1.63	14.28	10.21	19.52	15.07	17.73	7.45

NA Not Applicable.

<sup>1</sup> Body Weight Weight on the day of injection.

<sup>2</sup> Dose For dosage regimen, see Table 1.

<sup>3</sup> AUC Determined by trapezoidal rule. Cumulative to the last data point above zero concentration value.

<sup>4</sup> Cumulative to Day 4 for Month 1 and to Day 3 for Months 2 and 3.

<sup>5</sup> Average concentration between Day 4 and Day 24 (Month 1) or between Day 3 and Day 23 (Months 2 and 3).

<sup>6</sup> PK parameters of Group 6 are based on the first injection of the month.

Dose = Dose per injection

AUC<sub>0-24</sub> = AUC<sub>0-24h</sub>

[Sponsor's Vol.132 AT-03-05 (T1) Item 5, p. 649]

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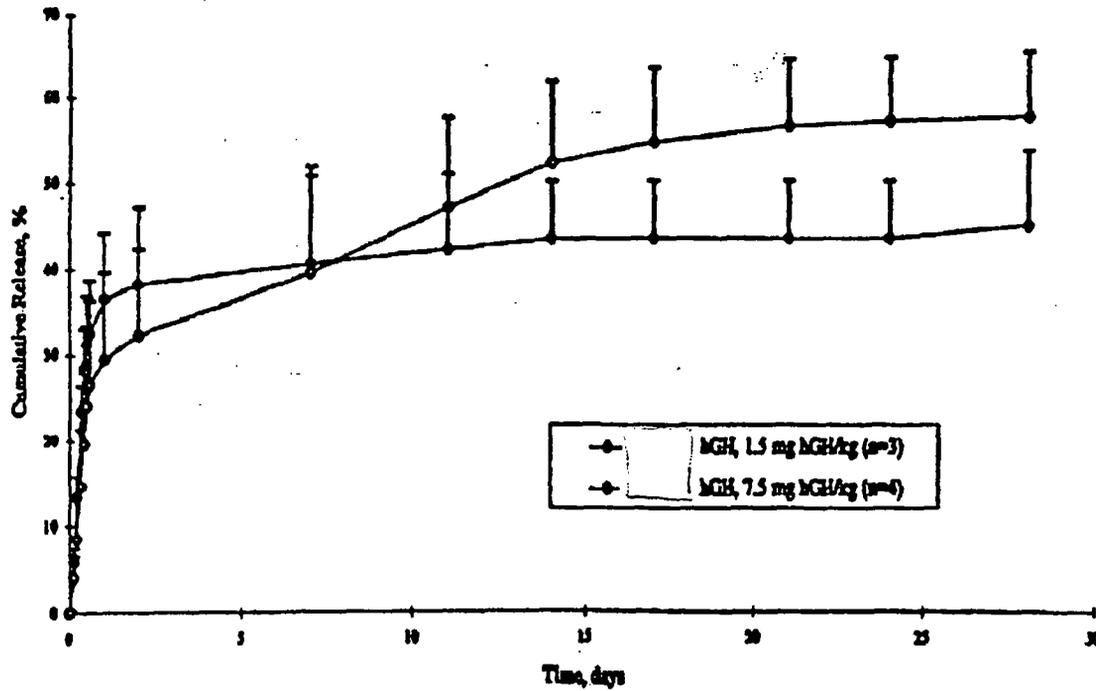
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NDA 21-075 p. 38

[Sponsor's Vol.1.3 AT-03-05 (T1) Item 5, p. 654]

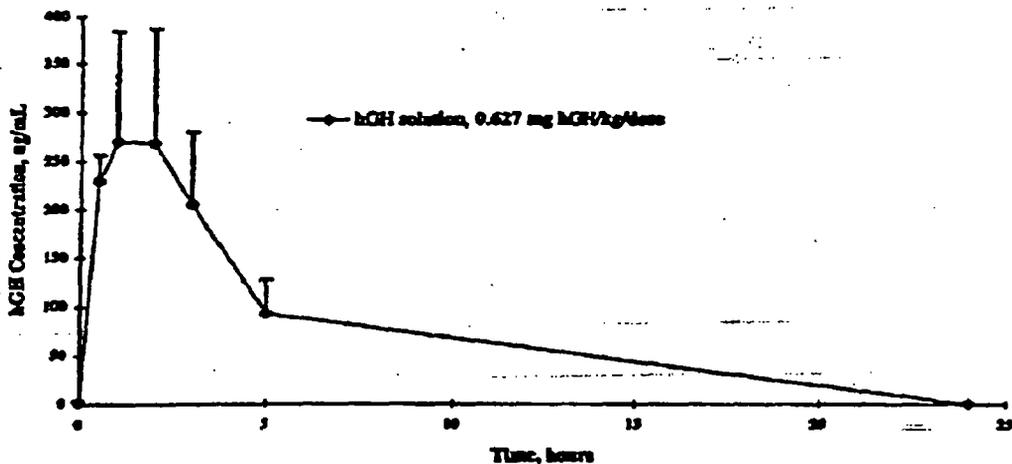
## One-Month Cumulative hGH Release Profiles in Rhesus Monkeys:

hGH  
(mean  $\pm$  SD)

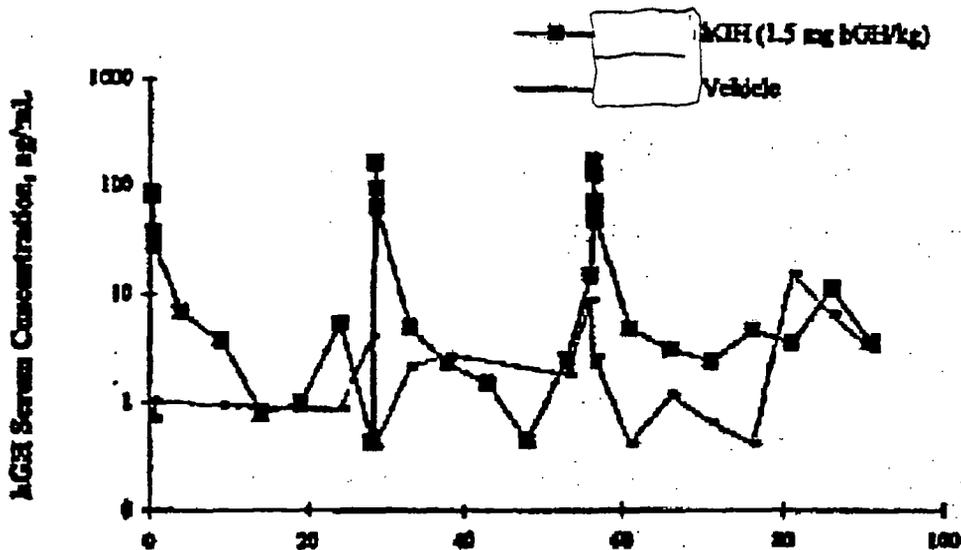


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[Sponsor's Vol.1.3 AT-03-05 (T1) Item 5, p. 653]  
**Serum Profile (0 to 24 hours) of Human Growth Hormone (hGH)  
in Rhesus Monkeys  
(mean  $\pm$  SD, n=4)**



**Three-Month Release Profile of  
High & Low Dose ProLease hGH in Rhesus Monkeys:  
hGH vs. Vehicle Control**  
[Sponsor's Vol.1.3 AT-03-05 (T1) Item 5, p. 656]



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## Comparison of Mean PK Parameters between the High and Low Dose [redacted] bGH

### AUC<sub>0-24</sub> ng/mL

	Vehicle	Low Dose		High Dose		% Increase <sup>d</sup>	
	Background <sup>a</sup>	Uncorrected <sup>b</sup>	Corrected <sup>b</sup>	Uncorrected	Corrected	Uncorrected	Corrected
Month 1	22	134	112	647	625	482	537
Month 2	53	229	176	1033	980	451	556
Month 3	143	242	99	1114	971	461	923

### C<sub>max</sub> ng/mL

	Vehicle	Low Dose		High Dose		% Increase	
	Background	Uncorrected	Corrected	Uncorrected	Corrected	Uncorrected	Corrected
Month 1	0.75	95	94	202	202	214	214
Month 2	0.40	180	180	290	290	161	161
Month 3	2.18 (0.00 <sup>b</sup> )	175	173	337	337	192	195

### C<sub>avg</sub> ng/mL<sup>c</sup>

	Vehicle	Low Dose		High Dose		% Increase	
	Background	Uncorrected	Corrected	Uncorrected	Corrected	Uncorrected	Corrected
Month 1	0.86 ± 0.13	3.55	2.69	14.28	13.42	402	498
Month 2	1.95 ± 1.40	2.32	0.37	19.52	17.56	841	4780
Month 3	4.22 ± 5.05	3.74	-0.48	17.73	13.51	475	na

### [redacted] Vehicle Background

AUC calculated by the trapezoidal rule, using the average of all non-zero values of the respective month

C<sub>max</sub> serum concentration at the nearest sampling point to the T<sub>max</sub> of the [redacted] bGH groups

C<sub>avg</sub> average of all non-zero values of the respective month

<sup>a</sup> Background levels observed in the [redacted] vehicle group were not subtracted.

<sup>b</sup> Background levels observed in the [redacted] vehicle group were subtracted.

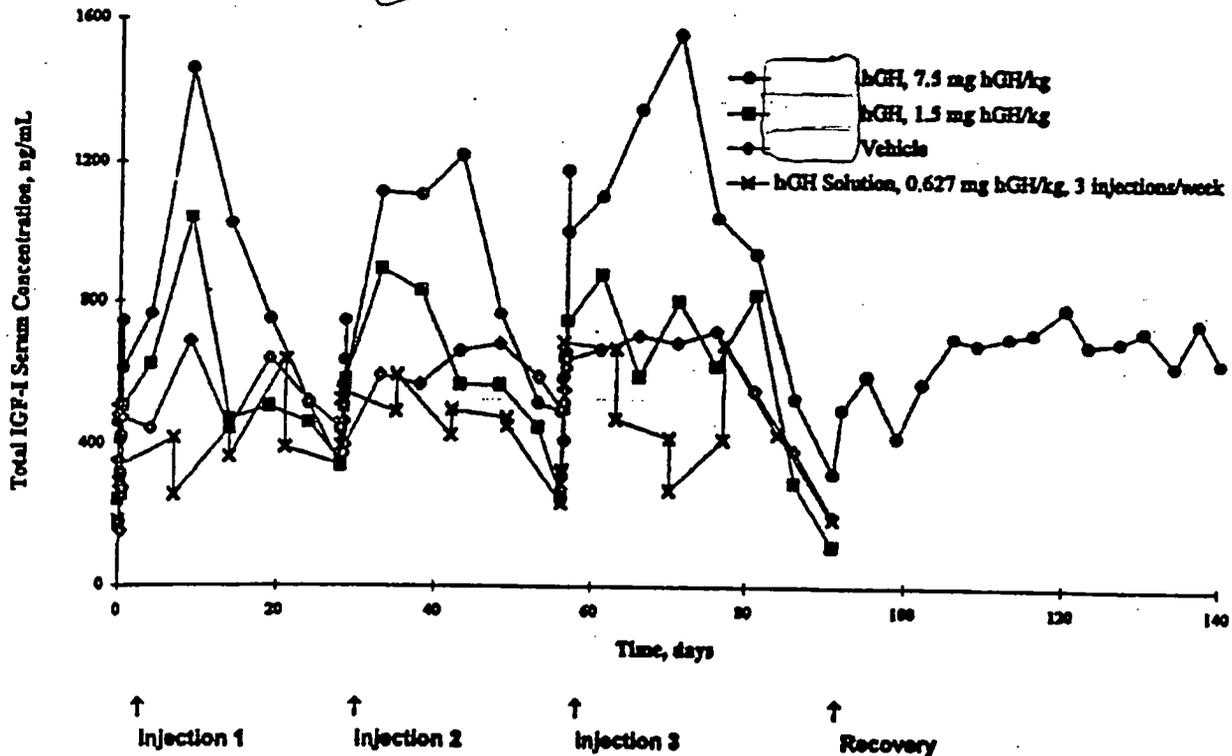
<sup>c</sup> % increase of the high dose [redacted] bGH group over the low dose group

<sup>d</sup> Background C<sub>max</sub> for the high dose [redacted] bGH: the high and low doses had different T<sub>max</sub>'s, and, therefore, the nearest time point to the high dose T<sub>max</sub> was chosen as the background for the high dose C<sub>max</sub>.

<sup>e</sup> C<sub>avg</sub> for [redacted] bGH is the average of Days 4-24 (Month 1) or 5-25 (Months 2 and 3).

[Sponsor's Vol.1.3 AT-03-05 (T1) Item 5, p. 658]

Three-Month Total IGF-I Serum Profile in Rhesus Monkeys:  
 [redacted] hGH vs. hGH Solution and Vehicle Control



The bioavailability for the two [redacted] hGH groups was reported to be 26% and 34% for the low and high dose groups, respectively, when it was estimated based on a previous IV study in juvenile rhesus monkeys ([redacted] 03-03). High dose [redacted] hGH values for  $C_{max}$ ,  $C_{avg}$ ,  $AUC_{(0-2days)}$ , and  $AUC_{(0-last)}$  were 388%, 374%, 405% and 632% of the low dose, respectively. These values are consistent with the nominal dosing multiple of 5, indicating linear pharmacokinetics within the dose range tested. The cumulative hGH release for the two [redacted] hGH groups were  $43 \pm 7\%$  (low dose) and  $58 \pm 8\%$  (high dose).

The percent increase for Months 1, 2, and 3  $C_{avg}$  and AUC values for the high dose [redacted] hGH group versus low dose group were 402%, 841%, and 475%, and 482%, 451% and 461%, respectively. (dosing multiple ca 5).

High dose [redacted] hGH resulted in 214, 161, and 192% increases over low dose [redacted] hGH in Months 1, 2, and 3, respectively. According to the sponsor the most reliable estimates of bioavailability (26-34%) and cumulative release (43-58%) were obtained in the one month segment when blood sampling could be conducted more frequently.

**NOTE:** hGH average background levels appeared to increase in the 2<sup>nd</sup> and 3<sup>rd</sup> months i.e.  $0.86 \pm 0.13$ ,  $1.95 \pm 1.40$  and  $4.22 \pm 5.05$  for Months 1, 2, and 3, respectively. Variability also increased. Whether or not this increase is due to the approach of puberty is unknown.

Both [redacted] hGH doses produced a sustained hGH release and an elevation in IGF-I levels. hGH release appeared to range from 1-3 days for the low dose and 17 to 19 days for the high dose.

Elevated IGF-I levels at the low dose ranged from ca 1-7 days and for the high doses ca 20-25 days. The pharmacokinetic disposition of hGH appeared to be independent of the dose and there did not appear to be a significant month effect on AUC and  $C_{avg}$  suggesting no accumulation in absorption, distribution or elimination of hGH for 3 months. [ $C_{max}$  changed significantly only between Month 1 and Month 2; the reason is not apparent.]

When the same amount of hGH (7.5 mg/kg/month) was administered to monkeys about 3 times higher and 20 times more sustained levels of total IGF-I were produced with [redacted] hGH than with three times weekly injections of hGH solution.

Three monkeys that received 3 monthly injections (one that received hGH and 2 that received high dose [redacted] hGH) produced anti-hGH antibodies.

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## Addendum 1

## Histopathology Inventory for NDA 21,075 [\* organ weight obtained]

Study	AI0305			
Species	Rhesus Monkey			
Adrenals	X*			
Aorta	X			
Bone Marrow smear	X			
Bone (femur)	X			
Brain	X*			
Cecum	X			
Cervix				
Colon	X			
Duodenum	X			
Epididymis	X*			
Esophagus	X			
Eye	X			
Fallopian tube				
Gall bladder	X			
Gross lesions	X			
Harderian gland				
Heart	X*			
Hypophysis				
Ileum	X			
Injection site	X			
Jejunum	X			
Kidneys	X*			
Lachrymal gland				
Larynx				
Liver	X*			
Lungs	X			
Lymph nodes, axillary (Gps 5,6,7,8)	X			
Lymph nodes submandibular	X			
Lymph nodes, mesenteric	X			
Mammary Gland	X			
Nasal cavity				
Optic nerves	X			
Ovaries				
Pancreas	X			
Parathyroid	X			
Peripheral nerve				
Pharynx				
Pituitary	X*			
Prostate	X			
Rectum	X			
Salivary gland, submandibular	X			
Sciatic nerve	X			
Seminal vesicles	X			
Skeletal muscle, thigh	X			
Skin	X			
Spinal cord, cervical, midthoracic,	X			

lumbar				
	X*			
Spleen				
Sternum, with bone marrow	X			
Stomach	X			
Testes	X*			
Thymus	X*			
Thyroid	X			
Tongue	X			
Trachea	X			
Urinary bladder	X			
Uterus				
Vagina				
Zymbal gland				

**IMMUNOTOXICOLOGY**

Study title: Immunogenicity Study of [redacted] Human Growth Hormone in Transgenic Mice Expressing rhGH.

Study No: and date: **AT-03-08** 8 Oct 96 Vol. 1.4 AT-03-08 (T2) Item 5 p. 1

Site and testing facility: The in-life phase of the immunogenicity study of [redacted] hGH in transgenic mice expressing rhGH was performed at [redacted] between Sep 95 and Jan 96.

GRP compliance: See QA statement.

QA- Report Yes ( ) No (X): This study was not conducted in accordance with GLP Regulations (21 CFR, Part 58) due to technical limitations imposed by the experimental design, such as generation of transgenic animals. It is reported that the study was performed according to the protocol and utilized the rigorous scientific standards of the testing facilities. Reported that the final report prepared by [redacted] has been reviewed by [redacted] Quality Assurance Department (signed).

Lot and batch numbers: Nutropin Depot, ~0.9 mg of rhGH in 6 mg of Nutropin Depot (contained a load of 16.1% hGH determined analytically) = Lot 0084;  
 Nutropin Depot Diluent (3% CMC, 01% Tween 20, 0.9% NaCl) referred to as [redacted] Vehicle = Lot 0136;  
 rhGH solution (Nutropin equivalent), 100 µg/mL, = Lot Nos. 95-062-2, 95-062-19a, 95-062-35a.  
 rhGH buffer = Lot Nos. 95-062-3, 95-062-19b, 95-062-35b.

**Methods:**

- Species/strain: hGH transgenic mice 2 – 10 mos. old [The hGH transgenic mice were offspring of transgenic males mated to Balb/c females.] Balb/c mice were included for comparison with the hGH transgenic mice.

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Dose Duration	Group	Mice Strain	Treatment	SC Dose Regimen	µg hGH per dose	µg µspheres per dose	Dose Vol (mL)	# Male	# Female
4-week	1	Balb/c	hGH solution	3x/week	10	-	0.2	6	7
	2	Balb/c	hGH	1x	120		0.2	7	6
	3	Transgenic rhGH	hGH solution	3x/week	10	-	0.2	7	8
	4	Transgenic rhGH	hGH	1x	120		0.2	7	8
12-week	5	Balb/c	hGH solution	3x/week	10	-	0.2	7	6
	6	Balb/c	hGH	3x	120		0.2	6	7
	7	Transgenic rhGH	hGH solution	3x/week	10	-	0.2	7	8
	8	Transgenic rhGH	hGH	3x	120		0.2	7	8
untreated	9	Balb/c	-	-	-	-	-	4	4
	10	Transgenic rhGH	-	-	-	-	-	6	3

[Sponsor's Vol. 1.4 AT-03-08 (T2) Item 5 p. 10]

Surviving mice were euthanized on either Day 100 or 101.

Mice received Nutropin Depot SC either once or once every 4 weeks for 3 cycles. SC doses of rhGH solution were administered 3 doses/week for either 4 or 12 weeks. The dose volume was 0.2 mL/injection for each treatment. Each dorsum (between the scapula) administration was at a separate location identified by a mark.

- Route of Administration: SC
- Rationale:

The purpose of this study was to evaluate the immunogenicity of Nutropin Depot following a single or repeated SC administration in transgenic mice expressing hGH. All transgenic mice were pre-screened for serum hGH levels and those animals that had an elevated hGH level were selected for the study. The Balb/c mice were included for comparison with the hGH transgenic mice. One nontreated group each of Balb/c mice and hGH transgenic mice were included for baseline evaluation. Animals were evaluated over approximately 3 months.

The rhGH transgenic mice model has been used previously to test the immunogenicity of rhGH (NDA 20-522 Report 91-283-0301).

- Number of animals/sex/dosing group See chart above
  - Endpoints: Blood samples were collected on Days -3, 16, 30, 51, 79, 93, and 100/101. Serum samples from selected days were analyzed for rhGH antibody by a [redacted]. The titer is expressed as the log of the dilution that produces a signal twice that of the negative control. The limit of quantitation in the assay is a titer of [redacted]. Any serum not exhibiting a signal at least twice that of the negative control at a dilution of 1:10 was considered to be negative. Sera producing a signal at least twice that of the negative control at a dilution of 1:10 or having a measured titer  $\geq 1.0$  were considered to be positive.
- Body weights, adverse symptoms, and injection sites were evaluated during the study.

**Observations:**

All hGH transgenic mouse sera were rhGH antibody negative following 4-week (Groups 3 and 4) and 12-week treatments (Groups 7 and 8) of rhGH or Nutropin Depot. Untreated animals (Groups 9 and 10) were also negative for rhGH antibody titer.

The rhGH antibody screen of Balb/c mice treated for 4 weeks with rhGH or Nutropin Depot (Groups 1 and 2) were positive (rhGH antibody titer of >1.0) beginning at Day 30 for 12/13 animals in Group 1 and for 7/13 animals in Group 2. By Day 100, the average titers of the animals exhibiting a positive response in Groups 1 and 2 were 1.8 and 1.4, respectively. Similar results were seen for the Balb/c mice treated for 12 weeks where 9/12 animals in Group 5 and 11/11 animals in Group 6 exhibited a positive rhGH antibody response starting at Day 30 and Day 51, respectively. Average titers of 3.4 and 3.7 were seen at Day 100 in animals exhibiting a positive response in Groups 5 and 6, respectively.

No significant effects were produced on body weights or adverse symptoms on injection sites. There were 26/69 mortalities distributed among untreated, rhGH solution and Nutropin rhGH groups as follows: 3/7M;1/8F in Group 3 (4-week, hGH); 4/7M;4/8F in Group 4 (single dose [redacted] hGH); 3/7M;4/8F in Group 7 (12-week hGH); 3/7M;2/8F in Group 8 (multiple dose [redacted] hGH); 2/6 M in Group 10 (untreated). [The life-span of transgenic mice is less than that of conventional mice.] There was only 1 Balb/c death - a Group 5 female on Day 4 attributed by the sponsor to incidental causes.

**Gross lesions:**

A number of transgenic and some Balb/c animals treated and untreated had body sores and/or swollen areas including genital regions in males and nipples in females.

Transgenic mice that died: Findings were mainly splenomegaly, hepatomegaly, diffuse/enlarged mammary gland, superficial granularity of the kidney, nodules/red foci of the lung, and epicardial mineralization. Deaths were attributed by the sponsor to those lesions that are known to occur spontaneously in hGH transgenic mice and reported as not due to test materials.

Terminal sacrifice: Similar to those seen in early death mice.

- **Timing:** Blood samples were collected on Days -3, 16, 30, 51, 79, 93, and 100/101. Serum samples from selected days were analyzed for rhGH antibody by a [redacted] assay.

**Overall Summary:**

Based on this study Nutropin Depot rhGH did not induce rhGH antibodies in transgenic mice expressing hGH. Balb/c mice that received Nutropin Depot developed anti-hGH antibody titers as did Balb/c mice that received an equivalent total dose of hGH solution for either 4 or 12 weeks.

**ProLease Diluent:**

**Study Title:** An Acute Local Tolerance Study of [redacted] Vehicles Administered Subcutaneously to Rabbits.

**Study No:** AT-03-09 [redacted] Study A074-716)

**Original NDA 21,075, Vol. 1.5 AT-03-09 (T1) Item 5 p. 1:**

**Conducting laboratory and location:** [redacted]

**Date of study initiation:** 16 Sep 96

**GLP compliance:** Yes

**QA- Reports Yes (X) No ( ):**

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NDA 21-075 p. 47

**Methods:** Each rabbit received single subcutaneous injections of the control (saline) and test materials in distinct sites on the dorsal area that was previously shaven. A 4<sup>th</sup> site (uninjected) was used as a comparative control. Four rabbits at each of 3 timepoints (3, 5 and 8 days) were sacrificed and the subcutaneous injection site areas (only) removed and processed for histopathological examination.

Animals were evaluated for changes in clinical signs and body weight, and the injection sites were examined and graded for any reaction to treatment.

**Dosing:** 2 ml/injection site

[Sponsor's Vol. 1.5 AT-03-09 (T1) Item 5, p. 5]

Group	Number of Males	Treatment	Dose Vol. (ml)	Day of Sacrifice
1	4	Control (untreated)	-	3
		Control (saline)	2	
		Vehicle 1	2	
		Vehicle 2	2	
2	4	Control (untreated)	-	5
		Control (saline)	2	
		Vehicle 1	2	
		Vehicle 2	2	
3	4	Control (untreated)	-	8
		Control (saline)	2	
		Vehicle 1	2	
		Vehicle 2	2	

**Species (Strain):** New Zealand White, Albino ELITE-NZW, rabbits [Has: (NZW) fBR]  
Ca 10 weeks of age; 2.68 to 3.49 kg

**Drug, lot #:**

**Formulation/vehicle:**

**Test Articles: ProLease Vehicles:**

Vehicle 1:  Dextran 70, 0.1% Tween 20, 0.9% NaCl  
Lot J05A6; Control 716H501-17

**Vehicle 2: [Chosen for NDA]**

3% carboxymethyl cellulose, 0.1% Tween 20, 0.9% NaCl  
Lot 0111; Control 716H501-18

Control: 0.9% Saline

**Observations and times:** Four rabbits at each of 3 timepoints (3, 5 and 8 days) were sacrificed and the subcutaneous injection site areas removed and processed for histopathological examination.

**Results:** There were no deaths or treatment-related clinical signs or effects on body weights.

There were a few incidences of erythema and local enlargement or swelling in a few rabbits of each group, including controls which appeared to be due to the physical presence of test material rather than inflammation. Microscopic examination showed an apparent  Vehicle 1 and 2 related presence of mixed inflammatory cells within the subcutaneous tissue of most injection sites (slightly more marked in  Vehicle 2 sites. No other discernible differences were reported to have been noted among treatment sites. [Scabs, focal epidermal necrosis, fragments of follicular structures within the dermis, focal inflammation of the skeletal muscle and hemorrhage were attributed to injection trauma.]

The local inflammatory infiltration reached a maximum in each vehicle-treated group on Day 5 and remained evident at the same  Vehicle 2) or reduced  Vehicle 1) incidence through Day 8. It is reported that the persistence of the local reaction through Day 8 appeared to be attributable to continuing phagocytic degradation of the high molecular weight compounds Dextran 70

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NDA 21-075 p. 48

and carboxymethyl cellulose in [redacted] vehicles 1 and 2, respectively. In general the vehicles were well tolerated.

## Summary:

Both vehicles appeared to induce a mixed inflammatory response (without necrosis or fibrosis) at most injection sites. [redacted] vehicle 2 produced a slightly more marked subcutaneous inflammation than [redacted] vehicle 1.

**Key findings:** There was a mixed inflammatory response (without necrosis or fibrosis) at most injection sites.

**Study Title:** An Acute Local Tolerance Study of [redacted] Formulation RG 502H [redacted] and 10K PLGA 50:50 [redacted] Administered Subcutaneously to Rabbits

Listed in Sponsor's Table of Contents Vol. 1.1 as study of PLG Microspheres.

**Study No:** AT-07-01 [redacted] Study A071-716]

Original NDA 21,075, Vol. #, 1.1 Tab T10 Item 5. At0701 p. 1

**Conducting laboratory and location:** [redacted]

**Date of study initiation:** 16 Sep 96 [Final Report 28 May 97]

GLP compliance: Statement -Yes

QA- Reports Yes (X) No ( ):

Methods

Each animal received single subcutaneous injections of the [redacted] vehicle (3% carboxymethyl cellulose, 0.1% Tween<sup>®</sup> 20, 0.8% NaCl) and both [redacted] formulations in distinct sites on the dorsal area that was previously shaven. A fourth site (uninjected) was identified and used as a comparative control. The day of dosing was designated as Day 1 of the study. The animals were evaluated for changes in clinical signs and body weight, and the injection sites were examined and graded for any reaction to treatment. Four animals at each of 2 timepoints (Days 4 and 8) were sacrificed and the subcutaneous injection site areas removed and processed for histopathological examination.

**General Comments:** The objective of the study was to determine the local tolerability of two [redacted] formulations RG 502H [redacted] and 10K PLGA 50:50 [redacted] administered subcutaneously to New Zealand White, albino ELITE-NZW [Haz: (NZW) fBR] rabbits. [Although not specifically stated, the designations [redacted] and [redacted] have been used previously to designate a [redacted] based polymer and an [redacted] Controlled Therapeutics [redacted] based polymer.] Stated that similar microspheres were used in studies AT-03-06 and AT-07-02.

A total of eight male New Zealand White, albino ELITE-NZW [Haz:(NZW)fBR] rabbits ca 10 weeks of age, weighing 2.95 to 3.27 kg were used.

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**Dosing:**

[Sponsor's Vol. 1.1 (T10) AT-07-01 Item 5, p. 5]

Group	Number of Males	Treatment	Dose (mg)	Dose Vol. (ml)	Day of Sacrifice
1	4	Control Untreated	-	-	4
		Vehicle Control	0	1	
		RG 502H	100	1	
		10K PLGA 50:50	100	1	
2	4	Control Untreated	-	-	8
		Vehicle Control	0	1	
		RG 502H	100	1	
		10K PLGA 50:50	100	1	

**Drug, lot #, [redacted] Formulations:**

RG 502H (BI) Lot 96-01-208-1; 10K PLGA 50:50 [redacted] Lot 96-01-208-2  
 [redacted] Vehicle Lots 0136 and 0111

**Formulation/vehicle:** [redacted] formulations were suspended in 1 ml [redacted] Vehicle (3% carboxymethyl cellulose, 0.1% Tween 20, 0.9% NaCl) just prior to injection.

**Observations and times:** Subcutaneous injection sites at Days 4 and 8

Grading of the microscopic findings was as follows: Minimal (+1), mild (+2), moderate (+3), and marked (+4).

**Results:****Day 4 Sacrifice:****Gross Necropsy:**

Red or pink foci were seen in 4/4 Vehicle controls.

Red foci, when identified histopathologically, corresponded to hemorrhage.

4/4 of each of the treatment formulations produced white foci - corresponded to multilocular irregular deposits of partially refractile test material.

**Histopathology: (Injection sites only.)**

Untreated control sites were within normal limits. Needle tracks/trauma of injection resulted in scabs, focal degeneration of skeletal muscle, focal/multifocal inflammation in the dermis and skeletal muscle and hemorrhage.

Vehicle controls were associated with subcutaneous cyst-like borders/spaces lined by fibroblasts - presumed by the sponsor to be the result of physical compression effects of the volumes injected. Surrounding subcutaneous tissue was loosely composed and variably infiltrated with inflammatory cells. No or minimal to mild subcutaneous inflammation (macrophages, lymphocytes, plasma cells, heterophils) was indistinguishable from normal background of subcutaneous untreated control sites.

Both test articles produced areas of a slight preponderance of heterophils with a few scattered giant cells. The severity of inflammation was moderate for all sites for both formulations. The two [redacted] formulations were indistinguishable. They showed as irregular, multilocular partially refractile deposits which were noted as foreign material within the subcutaneous tissue and occasionally, within the dermis or skeletal muscle.

All [redacted] formulation injection sites and all but 1 vehicle control injection site showed collagen compression.

**Day 8 Sacrifice:****Gross Necropsy:**

Two vehicle control sites showed red foci corresponding to hemorrhage. [redacted] injection sites of both formulations corresponded to multilocular irregular deposits of partially refractile test material. A tan foci and a green foci in two vehicle control sites were not presented microscopically.

#### Histopathology:

Subcutaneous injection sites of vehicle and [redacted] formulations showed minimal to moderate hemorrhage. Mild to moderate s.c. cyst-like borders/spaces (multiple and confluent in several sites) remained to Day 8 in all sites of vehicle controls and both [redacted] formulations.

Mild focal/multifocal fibrosis or condensation of connective tissue around generally discrete focal cyst-like borders/spaces was seen in 3/4 vehicle control sites.

Focal coalescence of loose connective tissue, fibrosis and granulation tissue surrounded or were admixed with cyst-like spaces of [redacted] formulations.

Both [redacted] formulations showed an indistinguishable inflammatory cell component characterized as granulomatous (contained an increased number of giant cells). The inflammatory cell reaction, which involved all subcutaneous sites, was generally moderate.

Residual collagen compression to some degree, as well as new collagen formation, was present in every injection site of vehicle and [redacted] formulations. One site of collagen formation was graded as minimal with the remaining 11/12 sites being mild.

**Summary:** Subcutaneous administration of the two [redacted] formulations was fairly well tolerated in rabbits after 8 days. No animals died and no treatment-related clinical signs, effects on body weights or treatment-related erythema were observed. Swelling or enlargement at injection sites was attributed to the physical presence (1 ml vol. per site) of test material within the subcutaneous area and not to a local tissue reaction. When present, the grossly observable findings of red or white foci corresponded to hemorrhage or the presence of [redacted] formulations, respectively. Microscopically, the two [redacted] formulations were indistinguishable within the subcutaneous sites. The moderate inflammatory response seen at Day 4 with both [redacted] formulations progressed by Day 8. Findings for the two formulations were indistinguishable. There was no evidence of tissue necrosis with either [redacted] formulation. Antibodies were not measured.

**Key findings:** Both [redacted] formulations produced similar clinical, macroscopic and microscopic responses at injection sites and were considered equivalent. According to the Sponsor, both [redacted] formulations produced a local reaction consistent with that reported in previous studies by [redacted] with similar microspheres and the local response was typical of that described by other investigators for PLGA microspheres.

## **OVERALL SUMMARY AND EVALUATION**

### **Introduction and Summary:**

Nutropin Depot is a sustained-release formulation of recombinant human growth hormone, which is indicated for the long-term treatment of patients with growth failure due to a lack of endogenous growth hormone secretion.

The formulation consists of micronized particles of rhGH embedded in biocompatible, biodegradable polylactide-coglycolide (PLG) microspheres (avg. diameter [redacted]) packaged in vials as a sterile, white to off-white, preservative-free, free-flowing powder. Before administration, the powder is suspended in aqueous Diluent for Nutropin Depot. The dosage and administration schedule (designed for s.c. administration once or twice monthly) should be individualized for each patient. The protein somatotropin, is synthesized by a specific laboratory strain of *E. coli* as a precursor consisting of the rhGH molecule preceded by the secretion signal from an *E. coli* protein.

In general this NDA describes a sustained-release form of the currently marketed Genentech somatropin product, Nutropin AQ® [somatropin (rDNA origin) injection], utilizing [redacted] a [redacted] Poly(D/L lactide co-glycolide) (PLG), the principal component of [redacted] technology, has a history of safe human usage in suture material, bone plates, and other sustained release drug products. [According to Makoto Miyajima et al. (Internat. J. Pharmaceutics, 169, No. 2, 255-263, 15 Jul 98), in recent years, much attention has been paid to biodegradable polymers as implantable reservoirs for sustained-release drug delivery, as these polymers do not require surgical removal after completion of drug release. Among these polymers, poly (lactic acid); (PLA) and copoly (lactic/glycolic acid); (PLGA) have been used as surgical sutures for the past 30 years and are known to be non-toxic and perfectly biocompatible. In addition, poly(lactide-co-glycolides) (PLGA) are widely investigated biodegradable polymers and copolymers. The biocompatibility of these polymers is well established and they have been extensively used in biomaterial applications such as tracheal replacement, ligament reconstruction, surgical dressings and dental repairs (Monica Ramchandani, et al., J. of Controlled Release, 43, Issue 2-3, 161-173, 18 Jan 97).]

Safety of [redacted] microspheres was also previously investigated in [IND [redacted] [redacted] ACTH) Pharm. Review dtd. 3 Sep 92 - attached]. Poly(D/L-lactide-co-glycolide) in the form of discs and microspheres were injected one time only in the flanks of rats. Sacrifice was on each of the following days: 1, 2, 4, 7, 14, 21, 60, 121, 184, and 365. Granulation of tissues at implant sites, fibrosis and inflammation of tissues were noted. It is reported however, that none of the test article sites in this study showed any toxic effects such as necrosis or unusual reactions uncommon to controls. References were provided under IND [redacted] demonstrating that lactic acid, the repeating subunit which comprises PLA polymer, occurs naturally in mammals and is converted, through normal metabolic pathways to carbon dioxide, glucose and glycogen.

Although we have no repeated preclinical chronic toxicity studies with [redacted] in this NDA, PLG microspheres as a pharmaceutical delivery system, are used in the U.S. in a sustained release formulation of LHRH (Lupron Depot - TAP Pharmaceuticals Inc.) and Sandostatin LAR® Depot - Novartis Pharmaceuticals Corp. Both of these marketed compounds are subject to long term use. After the [redacted] suspension is injected subcutaneously, the protein is released from the microspheres (initially by diffusion, followed by both polymer degradation and diffusion) into the subcutaneous space and absorbed. It is reported that the microencapsulation process has been shown by multiple analytical techniques to produce microspheres containing bioactive hGH without production of degraded forms (e.g. deamidated, oxidized or aggregated hGH). In due course, the microspheres undergo hydrolysis into small, naturally occurring molecules of lactic acid and glycolic acid, which are completely metabolized by the body.

The mechanism of action of Nutropin Depot is the same as that of the naturally occurring growth hormone. However, physiologically growth hormone is secreted in a pulsatile manner where as, after the initial burst, [redacted] hGH releases growth hormone in a prolonged sustained fashion. The effects on growth that this might have clinically are uncertain. Nutropin Depot treatment stimulates longitudinal bone growth and elevates insulin-like growth factor-1 (IGF-1) levels in a manner analogous to that observed with daily Nutropin [somatropin (rDNA origin) for injection] treatment.

The general pharmacological properties of growth hormone are well known and will not be discussed here. Complete reports for the studies performed using rhGH products formulated for daily administration have been previously submitted to NDA 20-168 (9 July 1993) and NDA 20-522 (9 November 1994).

Since the properties of growth hormone are well known and other Nutropin products are on the market, this NDA did not follow the standard battery of toxicology studies. Carcinogenicity, mutagenicity and reproduction studies were not conducted with Nutropin or Nutropin Depot and none are deemed necessary. In general safety relied on the marketed products as well as, a three-month study in monkeys, local tolerance studies in rabbits and monkeys, and an immunogenicity study in transgenic mice expressing hGH. Local tolerance studies of blank PLG Microspheres in rabbits (acute) and rats (single dose - chronic exposure) also add to the support of safety of [redacted] microspheres. The majority of submitted studies had to do with comparisons of pharmacokinetic and pharmacodynamic properties

between aqueous rhGH and Nutropin Depot or of various lots of drug which varied slightly from each other or which were produced in clinical, small or larger sized lots or batches during product development.

Release characteristics of Nutropin Depot in normal and immunosuppressed rats and in juvenile rhesus monkey showed release of rhGH from Nutropin Depot to occur in two phases: the first an initial rapid release phase is followed by a prolonged sustained-release phase.

Levels of hGH and IGF-1 following a single s.c. injection of Nutropin Depot indicated a dose response relationship. hGH serum concentrations were maximum during the first 24 hours after dosing followed by sustained elevated hGH levels that continued for 2-3 weeks after dosing.

One dose of Nutropin Depot per month for 3 months to rhesus monkeys showed slight increases in hGH and IGF-1 serum trough levels from Month 1 to Month 2. However, Month 3 showed no apparent further increases. Such findings would suggest no accumulation of rhGH.

In order to test for sustained-release of hGH without an excessively large immediate-release of hGH which would be unacceptable, various lots of Nutropin Depot manufactured at increasingly larger process scales were studied. There were some differences in the initial release phase of hGH with manufacturing process changes. Total hGH exposure and the pharmacodynamic response of total IGF-1 were in general comparable for the different processes.

Serum hGH concentration time profiles showed expected initial and sustained release phases in rats, monkeys and humans. All species showed rapid initial absorption of released rhGH. Rats and monkeys were the first to reach maximum ( $C_{max}$ ) concentrations which were also higher in these species as reflected primarily due to higher dose levels in these species. After the initial burst, hGH profiles became more similar in shape and terminal slope for about two weeks for all three species. [This is reported to be in contrast to the species-specific s.c. disposition profiles seen with rhGH solution.]

[It was reportedly shown in vitro that the initial 24-hour period represents rhGH released by diffusion from the microsphere surfaces and by initial hydration of the microspheres.]

Studies of Nutropin Depot in general showed an absence of systemic toxicity. Adverse effects appeared to be limited to a reversible local inflammation at the injection sites. Nonirritating local inflammatory reactions at injection sites in monkeys have been characterized by macrophage infiltration with a low level of diffuse interstitial fibrosis. There was a progressive resolution during study with complete recovery in monkeys by 3 months for the 1.5 mg rhGH/kg dose and 5 months for the 7.5 mg rhGH/kg dose. [Local tolerance could be of concern in humans.] Immunogenicity responses were relatively minor in monkeys, but severe in rabbits.

The monkey pharmacokinetic (PK) study was performed in juvenile Rhesus monkeys to mimic the juvenile population to which the drug will be administered. This study highlighted the two release phases as previously described i.e. an initial burst (diffusional) and a sustained-release phase.

Short term treatment of Nutropin Depot in hypophysectomized rats showed dose dependent increases in body weight and bone growth which were similar to that seen with daily rhGH administration. Nutropin Depot induced organ growth was more similar to that of continuous rhGH administration. However, the 3-month toxicokinetic study in primates showed no abnormal organ growth. The overall IGF-I response of the 7.5 mg rhGH/kg/dose (high dose) was greater than that of the 1.5 mg/kg dose (low dose) animals.

Nutropin Depot induces growth in hypophysectomized rats as well as, an elevated and prolonged IGF-I and IGFBP-3 responses (variable) in primates consistent with the known pharmacological activity of rhGH.

Three preclinical toxicological studies were performed with Nutropin Depot. In the rabbit tolerance study 300 mg microspheres containing 45 mg of rhGH in 3 ml of Nutropin Diluent were injected s.c. or i.m. The drug appeared to be fairly well tolerated through day 8. However, after a week anti-GH

antibody production resulted in a local immune-mediated inflammation reaction. All animals were anti-hGH antibody positive at 30 days at which time the tissue reaction to s.c. and i.m. [redacted] hGH injection in rabbits was greater than at 8 days. The Diluent and the microspheres without Nutropin appeared to be well tolerated.

Due to a vigorous antibody response to hGH and associated tissue effects in rabbits treated beyond one week, the rabbit did not appear to be a suitable model for long term local tolerance tests with this product and the 60 and 90 day [redacted] hGH groups were removed from the rabbit study (AT-03-06).

Juvenile monkeys (to simulate a juvenile human population) were dosed monthly for 3 cycles with 10 or 50 mg/kg Nutropin Depot which contained either 1.5 or 7.5 mg rhGH/kg. There were no signs of systemic toxicity and low levels of anti-GH antibody were detected only in 3 monkeys. A local tissue reaction consisting primarily of chronic inflammation and fine diffuse interstitial fibrosis was observed. By 140 days after administration, the microspheres and the local inflammatory response had resolved.

HGH transgenic mice were used to evaluate the immunogenicity of Nutropin Depot. No anti-GH antibodies were produced following 3 months of Nutropin Depot administration of 0.12 mg rhGH/dose or after 0.01 mg rhGH/dose of Nutropin AQ 3 times per week for up to 12 weeks.

Blank PLG microspheres were fairly well tolerated locally in an acute (Sacrifice days 4 and 8) s.c. study in rabbits and in a single dose - chronic exposure (365 days) s.c. study in rats. [Rat study: Pharm. Review of IND: [redacted] ACTH (dtd. 3 Sep 92) attached as part of Pharm. Review of IND [redacted] hGH (dtd. 3 Jul 96)]. In rabbits an inflammatory response was indistinguishable between two different formulations [RG 502 H [redacted] and 10K PLGA 50:50 [redacted]

#### Possible Safety Concerns:

##### Amount of microspheres vs. other products:

The amount of microspheres used in the product would not be expected to pose a problem since it is within range of or less than that of chronic use marketed products, which use poly(lactide-co-glycolide) microspheres.

##### Residual [redacted]

Of possible concern was the amount and safety of residual [redacted] in the final product. However, no problem would be expected since according to the reviewing chemist, the amount of residual [redacted] remaining in the product (<100 ppm) is less than that of the ICH permitted daily exposure (PDE) which for this class 2 solvent is [redacted] mg per day.

##### Zinc Exposure:

Reportedly histochemical analysis of the anterior pituitary has shown Zn<sup>++</sup> to be present in significant amounts in hGH secretory granules. Two Zn<sup>++</sup> ions complex reversibly with two molecules of hGH. To control the stability and solubility of hGH, it is encapsulated in the form of Zn-hGH complex in the Nutropin Depot fabrication process. Total exposure of zinc, expected to be in the range of about 1% of the Nutropin Depot dose, is much less than that of normal dietary absorption and would not be expected to pose a problem.

##### Inadvertent Intramuscular Administration:

Male rhesus monkeys (Study [redacted] 03-05) also received [redacted] hGH (small scale process) by the intramuscular (quadriceps femoris muscle) route to assess the performance in case of inadvertent intramuscular administration clinically to humans. The slight thickening seen grossly at the i.m. injections site of 1/4 monkeys which received [redacted] hGH proved histologically to be due to skeletal muscle degeneration. Inadvertent intramuscular administration would not be expected to pose an additional problem clinically.

Local Tolerance:

After a week, anti-GH antibody production in rabbits resulted in a local immune-mediated inflammation reaction, which became greater at 30 days when all animals were anti-hGH antibody positive. Monkeys were however, more tolerant. Dose sites of monkeys showed localized enlargements due to the physical presence of subcutaneous [ ] hGH and a local tissue reaction consisting primarily of chronic inflammation and fine diffuse interstitial fibrosis. These findings diminished over time.

Local adverse reactions would not be unexpected clinically. Adverse injection-site reactions reported clinically as mild to moderate have included erythema, pain during and post injection, nodules and lipoatrophy. Reportedly the lipoatrophy and nodules resolved over time. Thus, local tolerance problems could be a concern in humans.

Anti-hGH Response:

The anti-hGH response was severe in rabbits. However, the process and formulation selected for commercial development in general produced a minor anti-hGH response in rhesus monkeys. The titers were low and the incidences generally  $\leq 25\%$ . This finding is not unexpected since this is a heterologous peptide. Nutropin Depot rhGH did not induce rhGH antibodies in transgenic mice expressing hGH.

Minor anti-hGH responses have been noted clinically with this and other hGH products without consequence.

Accumulation:

One dose of Nutropin Depot per month for 3 months to rhesus monkeys showed slight increases in hGH and IGF-1 serum trough levels from Month 1 to Month 2. However, Month 3 showed no apparent further increases. Such findings would suggest no accumulation of rhGH.

The reviewing Medical Officer indicated that clinically, overall hGH and IGF-1 levels following Nutropin Depot s.c. administrations in GHD children were generally reproducible at each cycle with no evidence of accumulation during the course of 6 month studies ([ ]-03-002; [ ]-03-004).

Non-reversibility:

Although this drug appears to be safe for human use (based on preclinical studies), the drug is in a depot form and is non-retrievable once administered.

According to the reviewing Medical Officer, this would be of no concern at the doses used.

Possibility of Insulin Resistance:

The possibility of constant high levels of growth hormone resulting in insulin resistance was not investigated in animals.

According to the reviewing Medical Officer, insulin resistance was not a problem 6 months after therapy when investigated in a small clinical study.

Possibility of Development of Acromegaly:

The possibility of the development of acromegaly due to increased IGF-1 was not investigated preclinically.

However, the reviewing Medical Officer indicated that acromegaly would not be expected to happen clinically with the doses of Nutropin Depot administered.

Possibility of Stimulating Existing Tumor Growth:

This has been covered in the Labeling. The Contraindications section of the labeling states: Nutropin Depot should not be used in patients with active neoplasia. GH therapy should be discontinued if evidence of neoplasia develops.

**Labeling: [Pharmacology Section]**

**Carcinogenesis, Mutagenesis; Impairment of Fertility:** Carcinogenicity, mutagenicity and reproduction studies have not been conducted with Nutropin Depot.

**Pregnancy Category C:** Animal reproduction studies have not been conducted with Nutropin Depot. It is also not known whether Nutropin Depot can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nutropin Depot should be given to a pregnant woman only if clearly needed.

**Nursing Mothers:** It is not known whether GH is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Nutropin Depot is administered to a nursing mother.

Labeling, is the same as that for marketed Nutropin and Nutropin AQ. However the word "reproduction" in the Carcinogenesis, Mutagenesis, Impairment of Fertility section should be changed to the word "fertility".

**CONCLUSIONS and RECOMMENDATION: AP**

**External Recommendations (to sponsor):**

Carcinogenesis, Mutagenesis, Impairment of Fertility section of the labeling: The word "reproduction" should be replaced with the word "fertility".

cc: Original NDA 21-075; HFD-510 NDA 21-075; HFD-345;  
Original IND [redacted] HFD-510 IND [redacted]  
HFD-510 RSteigerwalt, DHertig, CKing

[redacted] /S/

David H. Hertig  
Pharmacologist

[redacted] /S/

*Concur*

11/10/99

**APPEARS THIS WAY  
ON ORIGINAL**

Herzig

IND [redacted]

28 June 1996

[redacted]

JUL 3 1996

Submission: 21,22 Nov 95; 14,18 Dec 95

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA  
Original Summary and Submission 14,18 Dec 95

[redacted] hGH

Recombinant Human Growth Hormone

Indicated Use: Treatment for growth hormone deficiency.

Related: pre-IND Meeting 13 Jun 95

Genentech: Nutropin (lyophilized) - IND [redacted] NDA 19-676

Nutropin Liquid - IND [redacted] NDA 20-522

(letter of authorization included)

[redacted] IND [redacted] - [redacted] ACTH

Supplier: hGH Bulk Solution - Genentech Inc.

polymers used in the manufacture of [redacted] [redacted]

KG

Formulation: The [redacted] hGH delivery system is composed of biodegradable microspheres containing bioactive hGH [ca. [redacted] (w/w)] and zinc carbonate incorporated into a matrix of unblocked [redacted] poly D/L lactide co-glycolide (PLG). Vehicle - [redacted] w/v carboxymethylcellulose sodium salt; [redacted] v/v polysorbate 20; [redacted] w/v NaCl; pH 7.

Proposed Clinical Trial:

The sponsor proposes to administer [redacted] hGH [0.75 mg/kg somatropin (5 mg/kg of [redacted] hGH) as a single subcutaneous dose] to healthy, growth hormone deficient adults (age  $\geq 18$  yrs) to assess the pharmacokinetics as well as safety. There are to be 12 adult patients of either sex with growth hormone deficiency defined as a peak growth hormone level of 5 ng/ml or less. The initial release phase of 24 to 48 hours duration and the sustained release phase extending to 28 days from administration are to be characterized. Safety assessments are to include effects on carbohydrate tolerance, insulin levels, glycosylated hemoglobins, assessment of antibody response to hGH, and assessment of injection sites. The formulation is intended to provide continuous release of growth hormone for up to 28 days. Safety assessment is to continue for a total of 56 days. (Continued next page.)

Table of Contents

	Lot #	Page
Preclinical Studies		
Rhesus Monkeys		
1 mo. Interim Toxicokinetic (AT-03-05)	0081c	2
Prelim. 2-Month Pharmacokinetic [redacted] 03-02)	0004, 0019, 0022	4
I.V. Pharmacokinetic [redacted] 03-03)	95-029-187	7
Rabbit		
S.C.; I.M. Tolerance (AT-03-06)	0084b, 0084d	7
Submission 14,18 Dec 95		8
Comments and Conclusions		9

cc: Original IND [redacted] HFD-345; HFD-510 RSteigerwalt  
HFD-510 IND [redacted] HFD-510 DHerig

[redacted] /S/ David H. Herig  
Pharmacologist

[redacted] /S/ 7/2/96

Serum levels of hGH, total IGF-I, and related binding proteins are to be measured to determine the duration and extent of sustained release of hGH and related biological effects.

Dose may be adjusted (downward or upward) after the first 4 to 6 patients are treated depending on the levels of growth hormone and IGF-I observed - goal to produce IGF-I levels within the age and sex adjusted range of normal. The maximum dose to be administered is to be 1.5 mg/kg somatotropin (10 mg/kg hGH) for the remaining 6 to 8 patients.

Preclinical Studies:

Interim (1 Month) Summary of a Three-Month Toxicokinetic Study of [redacted] hGH in Rhesus Monkeys: [redacted] 6403-108

[redacted] Study AT-03-05. Aug-Nov 1995. O.A. - Present.

- Lot: 0081a = fill vial 7.5 mg hGH in 50 mg [redacted] microspheres;  
 0081c = 30 mg hGH in 200 mg [redacted] microspheres;  
 95-029-169 = hGH solution - 5.1 mg hGH/ml  
 0111 = Vehicle - ca 3 ml/vial [3% w/v carboxymethylcellulose (sodium salt, low viscosity), 0.1% v/v Polysorbate 20 (polyoxyethylenesorbitan monolaurate) and 0.9% NaCl, USP]  
 Juvenile male rhesus monkeys (Macaca mulatta) were between 11-24 months old (1.9-3.2 kg). Dorsal cervical region injection sites.

Monkeys received a s.c. dose of [redacted] hGH or [redacted] hGH Vehicle in the dorsal cervical region once every 4 weeks for either one or three treatments. Treatment group designations and number of animals were as follows:

Study Duration	Group	Treatments	mg hGH /kg/dose	mg [redacted] /kg/dose	mL/kg /dose	# animals
1-month	1	[redacted] hGH Vehicle	0	0	0.33	4
	2	hGH Solution	0.627	0	0.123	4
	3	[redacted] hGH	1.5	10	0.33	4
	4	[redacted] hGH	7.5	50	0.33	4
3-month	5	[redacted] hGH Vehicle	0	0	0.33	4
	6	hGH Solution	0.627	0	0.123	4
	7	[redacted] hGH	1.5	10	0.33	4
	8*	[redacted] hGH	7.5	50	0.33	7*

\* Includes three recovery animals.

Only the 1-month segment of the study (Groups 1,2,3 and 4 will be presented in this summary.

Results:

Although there were some variations, in general no significant effects of test material were noted on clinical observations (other than site enlargements), body weight, food consumption, clinical chemistry, and organ weights. One low dose was sacrificed Day 26 due to apparent GI infection refractory to antibiotic treatment (various parameters were abnormal for this animal).

Non-irritating local enlargements were present at the s.c. injection sites. Group 4 enlargements were larger and persisted longer than those in Group 3. For Group 3 enlargements were either not observed or not measurable by Day 22 while for Group 4 except for one animal they were observed until the final observation day (Day 26).

Macroscopic findings at injection sites were limited to light color and/or red foci in the region of test material in all high dose and one low dose animal. Injection sites of two 0.627 mg hGH/kg animals had minimal or slight lymphohistiocytic infiltration in the subcutis, and one had minimal hemorrhage and fibrosis.

Microscopically [ ] hGH appeared as roughly spherical, nonstaining granular-to-amorphous bodies located focally in the subcutaneous compartment of all injection sites. [ ] hGH was associated with chronic inflammation which was more pronounced in the high dose (mild) than in the low dose (minimal). The inflammatory response was characterized by the presence of macrophages and occasional multinucleate foreign body giant cells. Sometimes the microspheres appeared as phagocytized intracytoplasmic bodies within the macrophages. The material did not appear to be cytotoxic to macrophages or any cells. Two high dose [ ] hGH monkeys showed a minimal infiltrate of lymphoplasmacytic cells. A minimal fibrosis was seen at the low dose with a slightly greater degree being seen in the high dose.

Total IGF-I values for controls ranged from [ ] ng/ml while that following [ ] hGH showed a slight increase for the low dose and a significant increase for the high dose. For the high dose group mean total IGF-I values were in excess of 450 ng/mL 0.5 hrs. post-dose until 28 days later (last sample collected). Peak levels ranged from [ ] ng/mL from 14 hrs. to 17 days post-dose. For the low dose, the total IGF-I concentrations exceeded 500 ng/mL at 12 hrs and 2 and 7 days post-dose; thereafter total IGF-I levels were within control ranges until termination. Compared to controls the hGH treatment group produced a marginal increase in total IGF-I with peak mean values of 320-450 ng/mL throughout the 4 weeks.

Up to 28 days post-dose anti-hGH antibody titer using an [ ] assay were negative.

The low dose [ ] hGH showed a maximum  $C_{max}$  of  $102 \pm 12$  ng/mL during the initial phase with an average hGH level of 2.36 ng/mL at 24 hrs. Thereafter hGH levels did not exceed the minimum detection limit of [ ] ng/mL. The high dose [ ] hGH exhibited  $C_{max}$  blood levels of ca  $396 \pm 143$  ng/mL and steady-state concentration ( $C_{ss}$ ) of 8.8 ng/mL Days 1-17. Day 17 (hGH 3.70 ng/mL) was the sampling day in which the limit of assay quantitation was exceeded by [ ] hGH groups. Cumulative percent releases for low and high [ ] hGH doses were 43 and 58% with bioavailability of 26 and 34%.

High dose [ ] hGH values for  $C_{max}$ ,  $C_{ss}$ ,  $AUC_{(0-2 \text{ days})}$ , and  $AUC_{(0-\infty)}$  were 388%, 373%, 405% and 632% of the low dose values respectively. [ ] hGH  $AUC_{(0-\infty)}$  values for the low and high dose groups were 44 and 278 ng/day/mL, respectfully which are agreeable with the dosing multiple of 5 thus showing linear pharmacokinetics in the dose range tested.

See Pharmacokinetic Study ( [ ] 03-02 - below) for Summary of PK Parameters for Study AT-03-05.

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Preliminary Summary of A Two-Month Pharmacokinetic Study with [redacted] Human Growth Hormone in Rhesus Monkeys: [redacted]

Study 03-02. March 1995. [total IGF-I analyzed by Genentech, Inc.; IGF-binding protein 3 analyzed by [redacted]]

Lots 0004, 0019, 0022 - 30 mg hGH in 200 mg [redacted] microspheres

Lot 0026 - [redacted] Vehicle

Lots 95-154-17A, 95-154-17B, 95-154-17C, 95-154-17D - 4 conc. hGH solutions

Treatment group designations and numbers of animals were as follows:

Treatments	Dose Regimen	hGH Dose (mg/dose)	hGH Dose Conc (mg/mL)	Dose Vol (mL/dose)	# animals
[redacted] hGH	single, Day 1	24	20	1.2	4
hGH solution	single, Day 1	24	20	1.2	4
hGH solution	28 daily	0.86	1.71	0.5	4
hGH solution	single, Day 1	3.6	7.2	0.5	4
hGH solution	28-day pump	20.4	13.2	1.55	4
[redacted] hGH Vehicle	single, Day 1	0	0	1.2	3

24 mg hGH is contained in 160 mg [redacted] hGH.

**Results:** Non-irritating variable sized enlargements at s.c. injection sites which generally became smaller with time and were not measurable by Day 32 were the only findings related to [redacted] hGH. Injection sites were collected 2 months post-dose at which time only 1 of 4 sites (ca 4 x 0.1 mm) was identified histologically. A few small cystic spaces (dia. <100  $\mu$ m) were surrounded by a mild granulomatous inflammatory reaction with the presence of small amounts of hGH immunoreactive material. Only one [redacted] hGH monkey was positive for anti-hGH antibody titer (Day 23 until end of study).

Pharmacokinetic studies showed two distinct patterns of hGH release, an initial release followed by a sustained release which was similar to monkeys receiving a single hGH injection (15% of total dose) followed by 28 days osmotic pump (simulating [redacted] hGH sustained release) delivery (85% of total dose). For the pump group  $T_{max}$  was  $0.10 \pm 0.04$  days,  $C_{max}$  was  $556 \pm 116$  ng/mL,  $AUC_{(0-2 \text{ days})}$  was  $200 \pm 53$  ng·day/mL,  $AUC_{(0-\text{last time point})}$  was  $534 \pm 137$  ng·day/mL. [redacted] hGH showed an initial hGH release ca. 24-36 hrs. post-dose followed by hGH sustained release up to Day 17, after which lower values were seen through Day 56. In this study (03-02) for [redacted] hGH (7.5 mg/kg) the  $T_{max}$  was  $0.44 \pm 0.04$  days and  $C_{max}$  was  $269 \pm 83$  ng/mL. [redacted] hGH showed a cumulative release of  $83 \pm 21\%$  vs  $95 \pm 19\%$  for the osmotic pump. [redacted] hGH bioavailability (based on 1.588 ng·day/mL AUC with 3.53 mg hGH i.v. - Study [redacted] 03-03) of  $49 \pm 13\%$  was similar to the  $56 \pm 11\%$  for the osmotic pump.

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The following Sponsor's table summarizes pharmacokinetic values for study [redacted] 03-02 and provides similar data for the toxicokinetic study AT-03-05:

Summary of PK Parameters

	hGH Dose (mg/dose)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (days)	C <sub>ss</sub> (ng/mL)	F(%)
[redacted] 03-02†					
[redacted] hGH (7.5 mg/kg)	24.00	269 ± 83	0.44 ± 0.04	7.89 ± 2.56	49 ± 13
hGH single SC bolus	25.88	2050 ± 405	0.11 ± 0.03	N/A	69 ± 12
hGH SC bolus + osmotic pump	20.77	556 ± 116	0.10 ± 0.04	14.92 ± 3.65	56 ± 11
hGH daily bolus (0.82 mg x 28 days)	22.96	176 ± 59	0.07 ± 0.02	N/A	88 ± 15
AT-03-05					
[redacted] hGH (7.5 mg/kg)	18.19	396 ± 143	0.25 ± 0.15	8.84 ± 6.10	34 ± 4.0
[redacted] hGH (1.5 mg/kg)	3.80	102 ± 12	0.19 ± 0.12	2.36 ± 2.05	26 ± 4.0
hGH three times a week (1.49 mg x 12 times)	17.88	319 ± 74	0.08 ± 0.03	N/A	122 ± 53

† Preliminary unofficial data.

All errors are ± standard deviation.

F is based on 158.88 ng day/mL AUC when dosed with 3.53 mg hGH [redacted] 03-03).

hGH concentrations were not corrected for background levels.

N/A Not applicable.

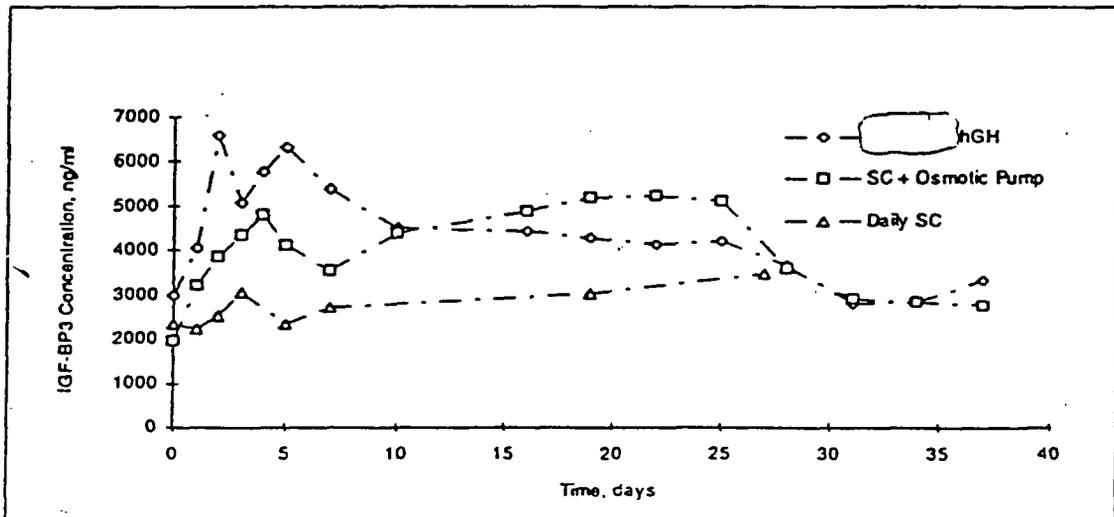
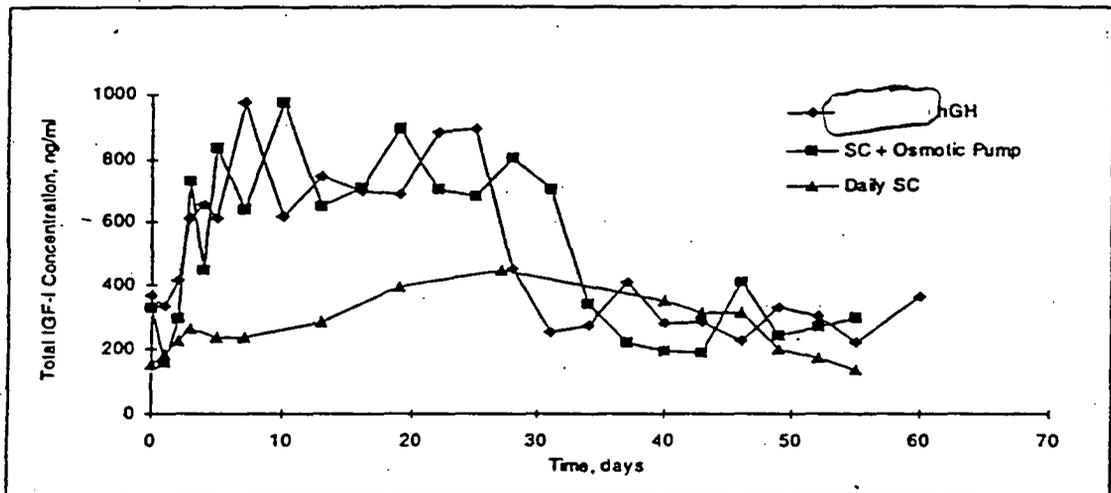
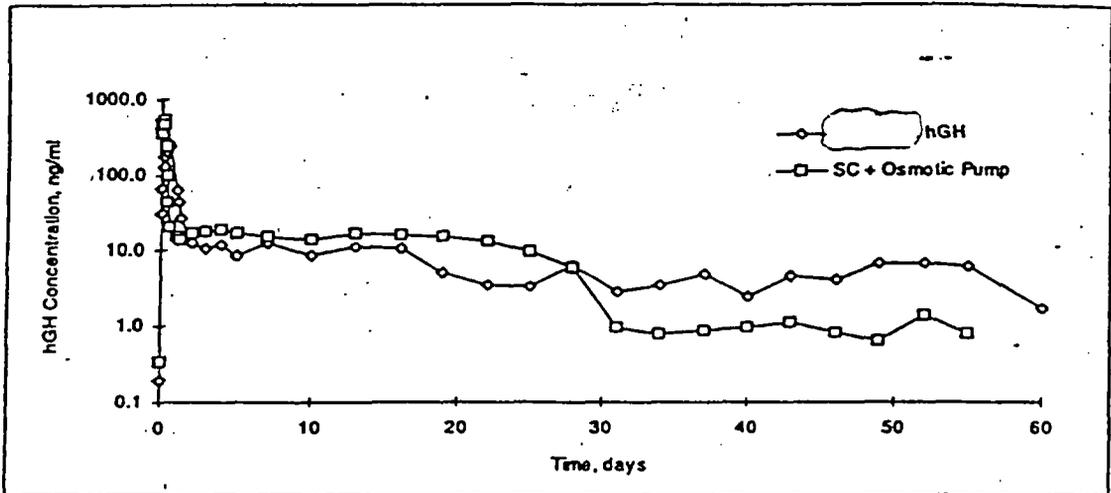
C<sub>ss</sub> values for [redacted] 03-02 are the average of hGH concentrations between 4-28 days post-dose.

C<sub>ss</sub> values for AT-03-05 low dose are the average of hGH concentrations at 24 hours post-dose and the high dose are the average of 1-17 days post-dose.

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Correlation of Serum hGH, Total IGF-I, and IGF-BP3  
(03-02)



hGH solution by a single injection and osmotic pump produced IGF-I levels of [ ] ng/mL from Days 4-32. [ ] hGH produced IGF-I levels about equivalent to that of the pump until Day 26 at which time the concentration decreased to 451 ng/mL on Day 29 after which baseline levels were reached.

hGH solution daily dosing produced total IGF-I values slightly higher or equal to baseline. [ ] hGH and hGH osmotic pump groups produced higher IGFBP-3 levels than the daily hGH dose group. The initial release phase produced peak IGFBP-3 levels of 6,565 ng/mL at 48 hrs for [ ] hGH and 4,811 ng/mL (Day 5) for the hGH single injection with osmotic pump group. The sustained release phase produced peak IGFBP-3 levels from ca [ ] ng/mL for Days 6-29 for the osmotic pump vs. [ ] between Days 4 and 29 for the [ ] hGH group. For the daily hGH dose group values ranged from [ ] ng/mL Days 2-28.

Intravenous Pharmacokinetic Study with Human Growth Hormone (hGH) in Rhesus Monkeys: [ ] Study 03-03.

Sep-Oct 1995. (hGH levels analyzed by [ ])

Lot 95-029-187 - hGH dose solution conc. 1.5 mg/mL

Lot 95-029-188 - Vehicle [ ] mg/mL NaCl, [ ] mg/mL phenol, [ ] mg/mL Polysorbate 20, [ ] mM sodium citrate, pH 6.0]

4 Juvenile male rhesus monkeys (2.2-2.3 kg) received 3 separate i.v. infusions each over a 5 min. period. Dose vol. was 1.0 mL/kg. Day 1 - Vehicle alone. Day 8 - low dose 0.15 mg/mL hGH solution. Day 15 - high dose 1.50 mg/mL hGH solution. Between dosing intervals were 7-days.

Results:

CL (systemic clearance) and Vdss (volume of distribution at steady state) values for the low dose were  $374.24 \pm 72.96$  mL/h/kg and  $119.44 \pm 24.88$  and for the high dose  $471.84 \pm 134.16$  mL/h/kg and  $138.81 \pm 48.42$  mL/kg. Mean AUC<sub>(0-∞)</sub> values were  $125.72 \pm 24.28$  ng·h/mL/kg ( $1773.16$  ng·h/mL/kg, normalized to 1.50 mg/kg) and  $1355.56 \pm 347.16$  ng·h/mL/kg for the low and high doses. The AUC<sub>(0-∞)</sub> was increased ca. 10 times from the low to high dose. [Linear pharmacokinetic disposition was suggested in the range of [ ] mg/kg hGH in juvenile rhesus monkeys.] The pooled AUC<sub>(0-∞)</sub> normalized for a dose of 3.53 mg hGH was 158.88 ng·d/mL. The half-lives, alpha HL/beta, HL/gamma, HL were  $0.06 \pm 0.03$ ,  $0.20 \pm 0.12$ , and  $0.26 \pm 0.03$  hour, respectfully for the low dose and  $0.07 \pm 0.03$ ,  $0.08 \pm 0.03$ , and  $0.52 \pm 0.21$  hour respectfully for the high dose.

It is reported that the pharmacokinetic parameter estimates between the two dosing levels were not significantly different and it was concluded that the pharmacokinetics of i.v. hGH was dose independent in juvenile rhesus monkeys.

A Subcutaneous and Intramuscular Tolerance Study (8 and 30-Day Segments) Following a Single Dose of [ ] hGH in New Zealand White Rabbits:

[ ] Study AT-03-06. Sept 1995. Antibody titer analysis by [ ] [Final Report to be filed later.]

Q.A.: Present.

Lot: 0084b, 0084d - Each vial of [ ] hGH contained ca. 49 mg hGH in 325 mg [ ]

0076 - Each vial of control [ ] microspheres contained 325 mg microspheres

0136 - [ ] hGH Vehicle contained ca. 3 mL/vial [3% w/v carboxymethylcellulose (sodium salt, low viscosity), 0.1% v/v Polysorbate 20 and 0.9% w/v NaCl, USP]

Dose: [ ] hGH 45 mg hGH (15% load) in 300 mg [ ] microspheres.  
Control: [ ] microspheres - 300 mg  
Vol 3 mL/injection site.

No. Animals: 6/group/phase male rabbits received either s.c. (dorsal region) or i.m. (biceps femoris muscles) test materials. Body weights 3352.0 - 3955.0 g

Necropsy was on Days 8 or 30.

Results: Observations showed no significant test material-related findings during 8 or 30-day intervals. Local enlargements directly related to the presence of test substance were seen at the s.c. injection sites of both treated and controls. The enlargements which varied in size diminished over the study course. Macroscopically the lesions generally consisted of localized reddening at, or close to, injection sites after 8 days (s.c. and i.m.) or after 30 days (s.c.). Test material was easier to identify at necropsy after 8 days than after 30 days.

Microscopic findings showed test material at most injection sites. Subcutaneous [ ] microsphere injection sites at 8 days showed minimal tissue reaction characterized mainly by macrophage infiltration and intralésional fibrosis without encapsulation. At this same time interval s.c. and i.m. [ ] hGH injection sites showed a similar mild severity tissue reaction. There was no evidence of cytotoxicity at s.c. sites. There was some myofiber degeneration in the i.m. [ ] hGH group which the sponsor theorizes may have been due to a localized compression of skeletal muscle fibers due to injected material rather than to a direct cytotoxic effect. They also suggest that the increased inflammation severity of [ ] hGH sites vs [ ] microsphere sites seen at 8 days may have been due to cellular infiltration probably associated with an early-stage immunologic response to hGH.

30-Day microscopic examination showed a mild tissue reaction with s.c. [ ] microspheres which was not significantly different from the minimal reaction found at 8 days. At 30 days the tissue reaction to s.c. and i.m. [ ] hGH injection was greater than at 8 days. Fibrosis was mostly unchanged but moderate to severe inflammation at injection sites was associated with prominent necrosis, heterophil degeneration, granuloma formation and diffuse plasmacytic and lymphocyte infiltration. The sponsor envisions this reaction to be enhanced by a local antigen-antibody reaction since all 30-day animals were anti-hGH antibody positive [log titers [ ] by a [ ] - there was no significant difference for the different routes. [Both s.c. and i.m. 8-day interval rabbits had titers less than the [ ] limit of quantitation except for 1 s.c. rabbit with a low titer of 1.4.] They concluded that the rabbit should not be considered an appropriate model for evaluation of local tolerance of [ ] hGH beyond the time at which significant antibody response is evident (due to administration of human protein to rabbits) and thus they conclude that 30 day rabbit data should not be used to evaluate local tolerance.

Submission: 12,14 Dec 95.

Per phone conversations 8,15 Nov 95 with Dr. M. Gary I. Riley, Director of Toxicology and Pharmacokinetics, and D. Hertig, FDA, it was requested that [ ] report to the FDA any unexpected findings at the 90-day interval of the primate toxicokinetic study. According to this submission, the three-month sacrifice occurred as planned on 27 Nov 95 and no significant or serious clinical findings were observed which would imply any safety concerns for clinical evaluation of [ ] hGH. Furthermore, at the three-month interval, no evidence of cumulative or residual local effects were observed for the [ ] hGH injection sites. Histological processing is underway, and the histopathological examination of tissues is scheduled.

Due to a vigorous antibody response to hGH and associated tissue effects in rabbits treated beyond one week (which according to the sponsor, appeared to invalidate the rabbit as a suitable model for long term local tolerance tests with this product) the 60 and 90 day [ ] hGH groups were removed from Rabbit Study AT-03-06.

Comments and Conclusion:

[ ] hGH is a sustained release formulation of recombinant human growth hormone encapsulated in microspheres made of the biodegradable polymer D/L lactide co-glycolide. The formulation is administered as an aqueous suspension injected subcutaneously and bioactive hGH is released from the depot for up to one month. The release of active drug is thought to occur by a combination of diffusion and erosion from the polymer implant. Analyses of encapsulated hGH is reported to show that the protein retains its biological and physico-chemical properties after the [ ] encapsulation process. It is reported that the microencapsulation process has been shown by multiple analytical techniques to produce microspheres containing bioactive hGH without production of degraded forms (e.g. deamidated, oxidized or aggregated hGH). The free-flowing powdered [ ] hGH Microspheres (avg. diameter ca [ ]) are suspended in an aqueous vehicle prior to subcutaneous injection.

[ ] hGH development is in partnership with Genentech Inc. Drug product lots for the clinical study have been manufactured using Genentech's recombinant hGH (somatropin, rDNA origin) which is also the active ingredient in Nutropin, a marketed compound.

Biocompatible, bio-degradable microspheres are formulated from poly-lactide co-glycolide (PLG) which has a history of safe human usage in suture material and bone plates. The PLG co-polymer ultimately, undergoes hydrolysis into small, naturally-occurring molecules which are completely metabolized by the body. PLG polymer degradation products, lactic acid and glycolic acid, should be easily metabolized and eliminated and would not be expected to pose a significant toxicity risk. The release phase is governed by the specific formulation and subtype of polymer used.

In vivo degradation rates of PLG polymers are reported to be inversely related to chain length, while unblocked polymers of a given molecular weight degrade more rapidly than their carboxy terminal blocked counterparts. The [ ] hGH formulation intended for clinical use is composed of a [ ] molecular weight unblocked polymer. Safety of [ ] microspheres were previously evaluated (IND [ ] Pharm. Review dtd. 3 Sep 92 - attached) using a 31 kD molecular weight blocked PLG polymer in a 12 month single dose s.c. study in rats. The local inflammatory reaction was reported to be similar in character and severity to that induced by discs of the same (31 kD) polymer but the reaction was of a shorter duration.

As a pharmaceutical delivery system, PLG microspheres are used in the US in a sustained release formulation of LHRH (Lupron Depot - TAP Pharmaceuticals Inc.).

The sponsor indicates that histochemical analysis of the anterior pituitary shows that  $Zn^{2+}$  is present in significant amounts in hGH secretory granules. Two  $Zn^{2+}$  ions complex reversibly with two molecules of hGH. In order to control the stability and solubility of hGH, hGH is encapsulated in the form of Zn-hGH complex in the [ ] hGH fabrication process. The sponsor indicates that the total exposure of zinc expected is ca. 1% of the [ ] dose and much less than normal dietary absorption. They further indicate that zinc elimination is proportional to intake and zinc elimination rates of ca. 3-5 mg/day have been recorded in normal adults.

According to the sponsor, the dose of [redacted] hGH to be used in this study would produce an anticipated initial release of ca. 20% (0.2 x 0.75 mg/kg) of hGH over the first 24 hrs. which would represent a dose of only 0.15 mg/kg. The release rate is anticipated to fall promptly after that period to a level of 2.0% of the total dose released per day, ca. 0.015 mg/kg/day.

Findings in general in monkeys showed injection sites to be limited to non-irritating local enlargements with histopathology findings of small cystic spaces (ca 100  $\mu$ m diameter) surrounded by a mild granulomatous inflammatory reaction after ca 2 months. Anti-hGH antibody was uncommon in the monkey, where as, in rabbits (which may not be suitable to evaluate local tolerance in this case) the reactions were more severe and all animals were anti-hGH antibody positive.

hGH, total IGF-I and IGFP-3 measurements showed [redacted] hGH to produce ca a one-month sustained release of hGH (an initial release phase followed by a sustained release phase).

From the standpoint of Pharmacology the proposed study may be permitted.

cc: Original IND [redacted] HFD-345  
HFD-510 IND [redacted]  
HFD-510 RSteigerwalt; HFD-510 DHertig

[redacted]  
David H. Hertig  
Pharmacologist

APPEARS THIS WAY  
ON ORIGINAL

21, 23 Apr 93

Name Change to: [redacted]

SEP 3 1992

3 September 1992

IND [redacted]

[redacted]

Submission: Received 16 July 1992

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA  
Original Summary

ACTH

Adrenocorticotrophic hormone, Corticotropin (9002-60-2)

Indicated Use: Exacerbations of Multiple Sclerosis

Related: DMF's: [redacted]

Supplier: Drug Substance Manufacturer - [redacted]

Formulation: The drug product is a homogenous mixture of ACTH and Poly (L-lactic acid) (PLA) polymer. ACTH is encapsulated into the polymeric microspheres as lyophilized micrometer particles. There are no covalent bonds formed between the two materials. Immediately before administration, the drug product is suspended in a vehicle.

Proposed Clinical Trial:

The sponsor proposes a study to define the duration of release of the delivery system in healthy male volunteers (assessed by plasma ACTH levels) as well as the pharmacodynamic activity of the released material (assessed by plasma cortisol levels). Twenty-four healthy male volunteers between 20-45 years of age are to be divided into three groups each containing 8 subjects. The dosing of each subsequent group is to be determined by the results of the previous groups. Subjects are to receive a single 20 mg (1.0 ml) dose of [redacted] ACTH by subcutaneous injection. In addition to blood samples, urines will be collected for analysis of urinary free cortisol and 17-hydroxy and 17-keto steroids.

Table of Contents

	<u>Lot #</u>	<u>Page</u>
Proposed Clinical Trial		1
Preclinical Studies	See studies	2-3
Literature References		3
Comments and Conclusions		3

cc: Original IND [redacted] HFD-345;  
HFD-510 IND [redacted] HFD-510 DHertig

[redacted] ISI  
David H. Hertig  
Pharmacologist

[redacted] ISI 9/3

Preclinical Studies:

The sponsor states (Graph only - of in-vitro ACTH release up to 50 days) that the properties of the polymer and the total amount of protein incorporated can be varied to change the total period of drug release from several days up to 2 months. They further state that there is no change in the biological activity of the ACTH after microencapsulation as determined by the USP potency assay (US Pharmacopeia XXII).

In Vivo Pharmacodynamics: [Only summary and graph of corticosterone conc. vs time up to 4 days for 2 microsphere ACTH and 3 soluble ACTH experiments in which the dose (?) of ACTH was roughly equivalent.]

It is reported that the pharmacodynamics of the [ ] ACTH microspheres were tested in vivo in rats and compared to the pharmacodynamics of an equivalent dose of soluble ACTH. Dexamethasone was used to suppress endogenous production of ACTH in the rat. Plasma corticosterone, the major steroid produced by rat adrenals, was followed with time as a measure of the biological activity of administered ACTH. Corticosterone elevation lasted about 1.5 to almost 2 times longer following [ ] ACTH injection than that of control rats receiving an equivalent dose of ACTH in water. Plasma corticosterone concentrations were greater for [ ] ACTH animals for the duration of the studies.

Development of Drug Delivery System:

365-Day Toxicity Test of [ ] ACTH Formulation [PLA (Poly, L-lactic acid) - Without ACTH] in Male Sprague-Dawley Rats: [ ] Project 89G-0102 Study Director [ ] Histopathology: [ ]

[ ] Lot/Batch - Not Given.

R.A. Signed: [ ] / Quality Assurance 8/10/90

Dose: Article I: PLA [discs and microspheres - Poly (L-lactic acid)]  
Article II: PLGA [discs and microspheres - Poly (D,L-lactide-CO-Glycolide)]

Routes of exposure were subcutaneous injection (0.3 ml - conc. 100 mg/ml) and implantation (1 x 5 mm discs).

Each animal, treated once on Day 0, received a subcutaneous injection (right flank) of the test material and a subcutaneous implant (left flank) of the same test material.

No. Animals and Groups: Young adult male Sprague-Dawley rats ca 6 to 7 weeks old.

PLA:

Groups 1-11 Treated - 6 animals per group.

Groups 12-22 Control - 2 animals per group.

PLGA:

Groups 1-11 Treated - 6 animals per group.

Sacrifice: Sacrifice of one treated group per regimen and one control group each of the following days: 1, 2, 4, 7, 14, 21, 28, 60, 121, 184, and 365.

Results:

Mortality:

One control on Day 2 - failed to recover from anesthesia. Animal 62 from Group II died Day 341 - cause of death appeared to be extension of teeth through the soft pallet.

Clinical Signs:

No signs of toxicity or infection were noted.

Body Weights: (Monthly Day 30-365 - Body weights were not recorded for animals sacrificed through Day 28.) Treated and controls gained weight during the course of the study.

Histopathology: Test article sites only.

Poly (L-lactic acid) implant disc sites: Common reactions included chronic inflammation, layer of mild tissue granulation around implant sites and phagocytic response.

Poly (L-lactic acid) injected spheres: Showed granulation of tissues at implant sites, fibrosis and inflammation of tissues.

Poly (D,L-lactide-CO-glycolide) disks and spheres: Similar to those above.

None of the test article sites showed any toxic effects such as necrosis or unusual reactions uncommon to controls.

Proposed Study:

Literature References and Reprints:

Clinical references included reprints on the status of ACTH therapy in multiple sclerosis. Reprints were submitted regarding biodegradable controlled-release parenteral systems which included biodegradable Poly (lactic acid) polymers. References also were provided demonstrating that lactic acid, the repeating subunit which comprises PLA polymer, naturally occurs in mammals and is converted, through normal metabolic pathways to carbon dioxide, glucose and glycogen.

Comments and Conclusion:

According to the sponsor, [ ] ACTH is a controlled release formulation designed to release up to 7 days of ACTH (adrenocorticotrophic hormone) which is encapsulated into injectable poly (L-lactic acid) (L-PLA) microspheres. L-PLA is a polyester that has been widely used in developing bone plates and is

reportedly well suited as a controlled release system.

Polyester degradation occurs by spontaneous hydrolysis of the ester linkages. The rate of polymer erosion is governed by changing polymer properties which influence water uptake. Biodegradable poly L-lactic acid microspheres left in the body space after drug release degrade to L-lactic acid an intermediate product during aerobic glycolysis or an end product under anaerobic glycolysis in humans. L-lactic acid is oxidized to pyruvic acid which can be further broken down to carbon dioxide and water or can be used to synthesize glucose. It is reported that since polymer degradation is by simple hydrolysis and not by enzymatic processes, the degradation rate should not be influenced by implantation in the body.

ACTH, a 39 amino acid peptide secreted by the anterior pituitary, acts to stimulate the adrenal cortex. Endogenous release of ACTH is normally stimulated by corticotropin releasing factor (CRF - inhibited by high levels of circulating cortisol) which is secreted by the hypothalamus. Clinically effects of ACTH are mainly related to stimulation of the production of glucocorticoids thus producing benefit in a variety of immunological and inflammatory disorders, including acceleration of resolution of the acute exacerbations which characterize multiple sclerosis.

There are no preclinical studies with the combination, however, except for hypersensitivity reactions, short-term administration of ACTH would not be expected to produce harmful effects, and Poly (L-lactic acid) and other polymers of this class have been relatively non-toxic when used with other drug combinations.

From the standpoint of Pharmacology, we would not anticipate any unexpected toxicity of the combination of Poly (L-lactic acid) and ACTH and thus would have no objection to initiation of the proposed clinical trial.

cc:  
Original IND [ ]  
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/S/

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