CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-426

PHARMACOLOGY REVIEW

2.16.05

PHARMACOLOGY AND TOXICOLOGY REVIEW

NDA #: 21-426

Product Name: Omnitrope-Lyophilized Powder

Sponsor: Biochemie GmbH, Kundl, Austria

Indication: Growth Failure

Division: Metabolic and Endocrine Drug Products

Reviewer: Herman Rhee, Ph.D.

Date: March 26, 2004

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EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability: Approval.

Pharmacology recommends approval of NDA21-426, based on the chemical confirmation of the structure of Omnitrop that is identical to hGH and the clinical data demonstrating growth in children.

1.2 Recommendation for nonclinical studies: None

1.3 Recommendations on labeling:

Carcinogenicity, Mutagenicity, Impairment of Fertility

Mutagenicity or carcinogenicity studies have not been conducted with Omnitrope.

Pregnancy: Pregnancy Category B
(Pregnancy labeling is identical to that for other FDA-approved GH products.)

Reproduction studies carried out with recombinant human growth hormone (rhGH) at doses of 0.3, 1, and 3.3 mg/kg/day administered SC in the rat and 0.08, 0.3, and 1.3 mg/kg/day administered intramuscularly in the rabbit (highest doses approximately 24 times and 19 times the recommended human therapeutic levels, respectively, based on body surface area) resulted in decreased maternal body weight gains but were not teratogenic. In rats receiving SC doses during gametogenesis and up to 7 days of pregnancy, 3.3 mg/kg/day (approximately 24 times human dose) produced anestrus or extended estrus cycles in females and fewer and less motile sperm in males. When given to pregnant female rats (days 1 to 7 of gestation) at 3.3 mg/kg/day a very slight increase in fetal deaths was observed. At 1 mg/kg/day (approximately seven times human dose) rats showed slightly extended estrus cycles, whereas at 0.3 mg/kg/day no effects were noted.

In perinatal and postnatal studies in rats, rh-GH doses of 0.3, 1, and 3.3 mg/kg/day produced growth-promoting effects in the dams but not in the fetuses. Young rats at the highest dose showed increased weight gain during suckling but the effect was not apparent by 10 weeks of age. No adverse effects were observed on gestation, morphogenesis, parturition, lactation, postnatal development, or reproductive capacity of the offsprings due to rh-GH. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing mother:

There have been no studies conducted with rh-GH in nursing mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when rh-GH is administered to a nursing woman.

PHARMACOLOGY/TOXICOLOGY REVIEW

3.1 INTRODUCTION AND DRUG HISTORY

A substantial body of preclinical data has been developed to support the safety of currently marketed rh-Growth Hormone (rh GH) products such as Humatrope, Genotropin, Norditropin, and Saizen. Pharmacology and general toxicology studies, including mutagenicity studies and reproductive toxicology, have documented the safety and efficacy of rhGH.

As agreed upon with FDA in a Pre-IND Meeting on 30 November 1998, BIOCHEMIE GmbH performed three nonclinical pharmacology and toxicology studies as presented subsequently.

- Rat weight gain bioassays in hypophysectomized male Wistar rats
- A subacute toxicology study in Sprague Dawley rats
- A local tolerance study in New Zealand White rabbits.

NDA number: 21-426
Review number: 0 00
Sequence number/date/type of submission: 000/July 30, 2003/Commercial
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Biochemie GmbH, Biochemiestraße 10 A- 6250 Kundl, Austria

Manufacturers for drug substance: There are two manufacturers:

Batches of BC rhGH drug substance bulk solution for clinical studies were manufactured according to current Good Manufacturing Practice (cGMP) by a contract manufacturer:

Covance Biotechnology Service Inc. 6051 George Watts Hill Drive P. O. Box 13865 Research Triangle Park, NC 27709-3865, U. S. A.

Batches for clinical studies were manufactured by Kundl and commercial batches of BC rhGH bulk solution are manufactured by BIOCHEMIE GmbH Biochemiestraße 10 A-6250 Kundl, Austria and [redacted] according to current Good Manufacturing Practices (cGMP).

Reviewer name: Herman Rhee, Ph.D.
Division name: Metabolic and Endocrine Drug Products
HFD #: 510
Review completion date: April 2, 2004

Drug:

Trade name: Omnitrope
Generic name: Human Growth Hormone, Somatropin, Somatotropin
Code name: EP2000 and BC rhGH

CAS registry number: 12629-01-05
Molecular formula/molecular weight: [redacted]
Structure: 191 amino acid residues that are identical to that of human GH

Relevant INDs/NDAs/DMFs: IND 58,980 (Somatropin), [redacted] NDA19-640(Humatrope), NDA19-721(Norditropin), NDA19-764(Saizen), and NDA20-280(Genotropin)

Drug class: Growth Hormone
Indication: Growth Hormone deficiencies

Clinical formulation: Omnitrope lyophilized powder 5.8 mg (17.4 IU) and 1.5 mg (4.5 IU), and Omnitrope Liquid 5 mg/1.5 ml (1.5 IU/1.5 ml)

Route of administration: Subcutaneous

Proposed use: Inadequate secretion of endogenous growth hormone
Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: Please see the subsequent reviews below.

3.2 PHARMACOLOGY

3.2.1 Brief summary

Human growth hormone has been used for many years without severe adverse effects. The biochemical mode of action of somatropin is well known and is extensively discussed in numerous publications. It involves two-site combination with a specific cell surface receptor, gene activation and the release of IGF-1 and the subsequent effects of the latter on a number of metabolic processes in the body.

3.2.2 Primary pharmacodynamics

In this section, rat weight gain bioassay data are presented.

Title: A 10-Day Efficacy Study Comparing 11 Different Formulations of Human Growth Hormone

Study#: 2000-3971/Laboratory Protocol#2000-3971
Report Date: March 16, 2001
Testing Facility: [redacted]

Purpose: To compare the efficacy of Omnitrope (EP2000) with international standard formulations in Wistar rats. Eleven GH products were tested.

Methods: Groups of 10 male hypophysectomized Wistar rats were given Omnitrope, Genotropin, or international reference standards of human somatropin at 5 or 10 µg/animal/day under GLP conditions as following: Control#1 and #2 were placebo vehicle (Batch/Lot#:991728) and somatropin (Batch/Lot#: NIBSC 98/574) and 11 different formulations of EP2000 (Batch/Lot# 45600305) were administered subcutaneously to the Wistar rats once daily for 10 days.

Treatment Groups	Dose level (µg/animal)	Dose Conc. (µg/mL)	Dose Volume (µl/animal)	No. of Animals (males)
1(Control*)	0	0	100	10
2 (Control**)	5	50	100	10
3 (TA #1)	5	50	100	10
4 (TA #2)	5	50	100	10
5 (TA #3)	5	50	100	10
6 (TA #4)	5	50	100	10
7 (TA #5)	5	50	100	10
8 (TA #6)	5	50	100	10
9 (TA #7)	5	50	100	10
10 (TA #8)	5	50	100	10
11 (TA #9)	5	50	100	10
12 (TA #10)	5	50	100	10
13 (TA #11)	5	50	100	10

* Group 1 (Control) received only the vehicle.
** Group 2 (Control) received the standard control solution of Human growth hormone NIBSC Lot# 98/574.
TA #1; EP2000, lot# 45600305, Bulk solution stored 8 weeks at 2-8 °C.
TA #2; EP2000, lot# 45600306, Bulk solution stored 8 weeks at 2-8 °C.
TA #3; EP2000, lot# 45600307, Bulk solution stored 8 weeks at 2-8 °C.
TA #4; EP2000, lot# 45600307
TA #5; EP2000, lot# B2066011-C, Bulk solution stored 12 months at -20 °C.
TA #6; EP2000, lot# S00100
TA #7; EP2000, lot# S00200
TA #8; EP2000, lot# S00500
TA #9; EP2000, lot# 551553A, Bulk solution stored 12 months at 2-8 °C.
TA #10; EP2000, lot# 0033440
TA #11EP2000, lot# 0034360

Results:

Mortality and Clinical Observation:
One rat from Group 12 (EP2000 lot # 0033440 at 5 µg/animal) was found dead on Day 10. There was no mortality following treatment with the vehicle, Somatropin or other 10 formulations EP2000. There were no clinical signs following treatment with the vehicle, Somatropin or the other 9 formulations EP2000. On Day 1 one animal 12004A (EP2000 lot# 0033440) was observed to have a slight to moderate decrease in activity and in some animals "cold to touch" was observed, which could not be clearly attributed to the treatment. Table 1 summarizes the clinical signs.

TABLE NO. 1 **CLINICAL OBSERVATIONS (REPORTED BY EXCLUSION)** **STUDY NO. 2000-3971**

GROUP 1: CONTROL (0.1M Ammonium bicarbonate 0 µg/animal)
GROUP 2: STANDARD CONTROL (Somatropin NIBSC 98/574 5 µg/animal)
GROUP 3: EP2000 LOT#: 45600385 (5 µg/animal)
GROUP 4: EP2000 LOT#: 45600386 (5 µg/animal)
GROUP 5: EP2000 LOT#: 45600387 (5 µg/animal)
GROUP 6: EP2000 LOT#: 45600307 (5 µg/animal)
GROUP 7: EP2000 LOT#: B2066011-C (5 µg/animal)
GROUP 8: EP2000 LOT#: S00100 (5 µg/animal)
GROUP 9: EP2000 LOT#: S00200 (5 µg/animal)
GROUP 10: EP2000 LOT#: S00500 (5 µg/animal)
GROUP 11: EP2000 LOT#: 551553A (5 µg/animal)
GROUP 12: EP2000 LOT#: 0033440 (5 µg/animal)
GROUP 13: EP2000 LOT#: 0034360 (5 µg/animal)

GROUP NO.	ANIMAL NO.	DAY	CLINICAL OBSERVATIONS
1	1003A	6	Few red spots on right pinna
3	3002A	-2, 1	Slight opacity of left eye
	3005B	-3	Slight opacity of right eye
5	5001A	11	Slight activity decrease (8:53) Whole body cold to touch (8:53)
6	6002A	1, 8-9	Slight opacity of right eye
	6005B	-1 4 7	Moderate opacity of right eye Moderate opacity of both eyes Moderate opacity of right eye
	6009C	10-11	Moderate opacity of right eye
7	7007B	5-6	Few red spots on right pinna
8	8001A	6-7	Few red spots on right pinna

Body Weights: Statistically significant increases (approximately 2 to 3 fold) in mean body weight gain were observed in all EP2000 formulation and Somatropin dosed animals. The increase in body weight gain was similar and no statistical difference was noted between EP2000 and Somatropin treated animals as presented partially in a Table 3 below.

TABLE NO. 3 **BODY WEIGHT (% CHANGE) AND POTENCY LEVELS COMPARED TO GROUP 2 (IU/mg)** STUDY NO. 2000-3971

GROUP 2: STANDARD CONTROL (Somatropin NIBSC 98/574 5 µg/animal)
GROUP 3: EP2000 LOT#: 45600305 (5 µg/animal)
GROUP 4: EP2000 LOT#: 45600306 (5 µg/animal)
GROUP 5: EP2000 LOT#: 45600307 (5 µg/animal)
GROUP 6: EP2000 LOT#: 45600307 (5 µg/animal)
GROUP 7: EP2000 LOT#: B2066011-C (5 µg/animal)
GROUP 8: EP2000 LOT#: S00100 (5 µg/animal)
GROUP 9: EP2000 LOT#: S00200 (5 µg/animal)
GROUP 10: EP2000 LOT#: S00500 (5 µg/animal)
GROUP 11: EP2000 LOT#: 551553A (5 µg/animal)
GROUP 12: EP2000 LOT#: 0033440 (5 µg/animal)
GROUP 13: EP2000 LOT#: 0034360 (5 µg/animal)

GROUP NO.	ANIMAL NO.	% CHANGE				GROUP NO.	ANIMAL NO.	% CHANGE			
2	2001A	12				5	5001A	7			
2	2002A	16				5	5002A	17			
2	2003A	16				5	5003A	10			
2	2004A	23				5	5004B	22			
2	2005B	16				5	5005B	21			
2	2006B	15				5	5006B	19			
2	2007B	18				5	5007B	21			
2	2008C	27				5	5008C	26			
2	2009C	18				5	5009C	25			
2	2010C	19				5	5010C	16			
Mean		18.00				Mean		18.40	Potency:	3.07	IU/mg
SD		4.27				SD		6.11	SD:	0.40	
Variance		18.22				Variance		37.38	C.I. (95%):	2.29 -	3.85
N		10				N		10			
3	3001A	19				6	6001A	12			
3	3002A	20				6	6002A	15			
3	3003A	16				6	6003A	17			
3	3004B	15				6	6004A	21			
3	3005B	19				6	6005B	24			
3	3006B	17				6	6006B	19			
3	3007B	23				6	6007B	18			
3	3008C	21				6	6008C	29			
3	3009C	17				6	6009C	26			
3	3010C	21				6	6010C	23			
Mean		18.80	Potency:	3.13	IU/mg	Mean		20.40	Potency:	3.40	IU/mg
SD		2.53	SD:	0.27		SD		5.21	SD:	0.37	
Variance		6.40	C.I. (95%):	2.60-	3.66	Variance		27.16	C.I. (95%):	2.67 -	4.13
N		10				N		10			
4	4001A	10				7	7001A	8			
4	4002A	21				7	7002A	17			
4	4003A	18				7	7003A	19			
4	4004A	20				7	7004B	23			
4	4005B	19				7	7005B	8			
4	4006B	24				7	7006B	25			
4	4007B	13				7	7007B	23			
4	4008C	12				7	7008C	18			
4	4009C	22				7	7009C	25			
4	4010C	26				7	7010C	14			
Mean		18.50	Potency:	3.08	IU/mg	Mean		18.00	Potency:	3.00	IU/mg
SD		5.30	SD:	0.36		SD		6.38	SD:	0.40	
Variance		28.06	C.I. (95%):	2.37 -	3.79	Variance		40.67	C.I. (95%):	2.22 -	3.78
N		10				N		10			

Mean, standard deviation, variance and potency reported at 2 decimals for statistical purposes only

Gross Histopathology: No treatment related findings were observed, although incidental observations were noted as in Table 4. Successful hypophysectomy procedure for the experimental animals was confirmed during necropsy.

TABLE NO. 4 **MACROSCOPIC FINDINGS** **STUDY NO. 2000-3**

GROUP 1: CONTROL (0.1M Ammonium bicarbonate 0 µg/animal)
GROUP 2: STANDARD CONTROL (Somatropin NIBSC 98/574 5 µg/animal)
GROUP 3: EP2000 LOT#: 45600305 (5 µg/animal)
GROUP 4: EP2000 LOT#: 45600306 (5 µg/animal)
GROUP 5: EP2000 LOT#: 45600307 (5 µg/animal)
GROUP 6: EP2000 LOT#: 45600307 (5 µg/animal)
GROUP 7: EP2000 LOT#: B2066011-C (5 µg/animal)
GROUP 8: EP2000 LOT#: S00100 (5 µg/anim
GROUP 9: EP2000 LOT#: S00200 (5 µg/anim
GROUP 10: EP2000 LOT#: S00500 (5 µg/anim
GROUP 11: EP2000 LOT#: 551553A (5 µg/anim
GROUP 12: EP2000 LOT#: 0033440 (5 µg/anim
GROUP 13: EP2000 LOT#: 0034360 (5 µg/anim

GROUP NO.	ANIMAL NO.	MACROSCOPIC FINDING
1	1001A	No significant findings
	1002A	No significant findings
	1003A	No significant findings
	1004B	No significant findings
	1005B	EPIDIDYMIS Enlargement: bilateral TESTIS Enlargement: bilateral
	1006B	KIDNEY Dilatation: pelvis, right
	1007B	THYMUS Dark area: red, many
	1008C	EPIDIDYMIS Enlargement: bilateral PROSTATE Enlargement SEMINAL VESICLES Enlargement: bilateral TESTIS Enlargement: bilateral
	1009C	No significant findings
	1010C	EYE Pale area: many, cornea, right THYMUS Dark discoloration: red, many
2	2001A	No significant findings
	2002A	No significant findings
	2003A	THYMUS Dark area: many

Conclusion: Eleven EP2000 formulations increased body weight gain when compared to animals receiving the vehicle control. According to the rat weight gain data Omnitrope EP2000 formulations had comparable effects to the international standards and Somatropin on body weight gain as shown below..

Results of the rat weight gain assays

Study no.	Batch no.	Reference standard	Results
980150	B-2083005-C, 3056-CV38V01	NIBSC 88/624	One control and 2 treated animals died on different days during the experiment for no apparent reason. The deaths are not considered to be related to treatment because they are scattered between the groups. There was a significant increase in body weight gain in all treated groups, which was identical in those receiving Omnitrop and the reference standard. There was no clinical sign of irritation at the sites of the repeated local injections. It was concluded that the 2 preparations had the same activity as a 'Growth Hormone'.
991132	582553A, B-2066012-C, B-2066006-C	NIBSC 88/624	All treated animals gained weight and there was no significant difference between the effects of the reference and test preparations. There was no clinical evidence of local intolerance of the injections.
2000-0491	594403A, 594353A, 592003A, Genotropin lot 26491 A51	NIBSC 88/624	All treated animals gained weight to the same extent. The lots of Omnitrop, NIBSC 88/624 and the marketed recombinant product Genotropin® were indistinguishable.
2000-2841	45600304, 45600305, 45600306, B-2066011-C (stored 8 weeks at 2-8°C), 0026069	NIBSC 88/624 and NIBSC 98/574	There was the same significant increase in body weight in all the treated groups. No clinical features of an injection site reaction were noted.
2000-3971	45600305, 45600306, 45600307 (bulk solutions stored 8 weeks at 2-8°C), 45600307, B2066011-C, S00100, S00200, S00500, 551553A (stored 12 months at 2-8°C), 0033440, 0034360	NIBSC 98/574	Treatment-related clinical signs were observed in one animal from two groups (lots 45600307 and 0033440) on Day 11 and included slight to moderate decrease in activity, animal lying on cage floor, labored respiration and whole body cold to touch. There were no treatment-related clinical signs observed following the administration of the vehicle, Somatropin or with the different formulations of Omnitrop. The clinical signs could not be clearly attributed to treatment due to the very low incidence for these formulations. There was the same significant increase in body weight in all the treated groups.

Abuse liability: NA

3.3 PHARMACOKINETICS/TOXICOKINETICS

The sponsor presented the following table for pharmacokinetic data from the 2-week rat toxicology study (Study#981106, See Appendix 1, IND58,980).

Pharmacokinetic parameters	Toxicokinetic study in rats		Pharmacokinetic studies in healthy volunteers(1)
Dose	2 mg/kg ≈ 0.6 mg	8 mg /kg ≈ 2.4 mg	5 mg (≈ 0.07 mg/kg)
C_{max} (µg/L)	60 ± 30	78 ± 18	50 ± 15
t_{max} (h)	2.5 ± 1	5.5 ± 1	4 ± 1.5
AUC (h · µg/L)	240 ± 100	400 ± 90	400 ± 50

(1) Report of human bioequivalence study EP2K-99-PhIUSA

3.3.1 Brief summary

In healthy adult subjects, tmax of GH was reached 4 hours after administration and the mean elimination half-life is approximately 2.5 hours. Omnitrope clearance is approximately 13 L/h and within 24 hours the hormone blood level returned to baseline. Available literature data suggest that GH clearance is similar in GHD pediatric and adult patients. No pharmacokinetic studies have been performed in pediatric subjects.
PK parameters:

Table 1: Pharmacokinetic parameters of somatropin determined from the three Phase I studies. Results are presented as mean ± SD

	EP2K-99-PhISUSA	EP2K-99-PhIUSA		EP2K-00-PhI[^Q]	
		Omnitrop	Genotropin®	Omnitrop	Omnitrop Liquid
t_{lag} (h)	0.7 ± 0.5				
C_{max} (µg/L)	37 ± 9	52 ± 21	48 ± 20	*55 ± 13	*52 ± 10
t_{max} (h)	3.6 ± 0.5	4.1 ± 1.6	4.9 ± 1.8	3.9 ± 1.8	3.5 ± 1.3
AUC_{inf} (h*µg/L)	291 ± 42	416 ± 110	400 ± 105	*456 ± 44	*426 ± 45
Ka (h^{-1})	0.4 ± 0.2				
$t_{1/2}$ (h)	2.4 ± 0.4	2.7 ± 0.6	2.9 ± 0.6	2.4 ± 0.6	2.4 ± 0.7
CL/F (L/h)	18 ± 3	13 ± 3	13 ± 4		
90% confidence intervals		Log C_{max}: 98 → 117 Log AUC_{inf}: 100 → 108		Log C_{max}: 90 → 99 Log AUC_{inf}: 90 → 97 t_{max}: 82 → 116	
ANOVA (p)		Log C_{max}: 0.2 Log AUC_{inf}: 0.1			
Wilcoxon test (p value)		t_{max}: > 0.05			

* Geometric mean

Table 2: Effect of gender on the pharmacokinetic parameters of somatropin determined from the EP2K-99-PhISUSA and EP2K-99-PhIUSA studies (mean)

	EP2K-99-PhISUSA			EP2K-99-PhIUSA					
	Omnitrop			Omnitrop			Genotropin®		
	Female	Male	Kruskal-Wallis (p value)	Female	Male	Kruskal-Wallis (p value)	Female	Male	Kruskal-Wallis (p value)
t_{lag} (h)	0.8	0.6	0.7						
C_{max} (µg/L)	40	33	0.2	61	43	0.08	56	40	0.06
t_{max} (h)	3.7	3.5	0.8	4	4	0.5	5	5	0.5
AUC_{inf} (h*µg/L)	311	270	0.1	465	366	0.04	453	346	0.01
Ka (h^{-1})	0.5	0.4	0.7						
$t_{1/2}$ (h)	2.3	2.5	0.5	3	3	0.2	3	3	0.08
CL/F (L/h)	16	19	0.1	11	14	0.05	12	15	0.02

3.4 TOXICOLOGY

3.4.1. Overall toxicology summary

The toxicology program was limited to a 14-day subacute toxicology study in rats and a 7-day local tolerance study in rabbits according to the Pre-IND meeting recommendations (dated Nov. 30, 1998). Both the lyophilized and the liquid formulations were tested, which demonstrated that Omnitrope had effects similar to authentic rhGH. No additional data were presented by the sponsor because chemical characterization and bioassay demonstrated Omnitrop is identical to hGH in structure and activity.

In summary, ten Sprague-Dawley rats/sex/group received Omnitrope 0, 2, and 8 mg/kg/day subcutaneously for 14 days. PK data were analyzed on Days 1, 7 and 14. There were no abnormal clinical signs during the study. No reaction at the sites of the injections was seen. Treated females showed a dose-related increase in weight gain and food consumption, although the parameters were unchanged in males. There were no remarkable hematological or clinical chemistry observations, although there were decreases in ALT and AST and an increase ALP, as well as a fall in serum albumin. There were slight increases in relative heart and kidney weight in females but not in males. There were no clear histopathological abnormalities that were induced by the treatment with Omnitrope.

General toxicology: The sponsor depends largely on previously published data.

Genetic toxicology: Mutagenicity studies were not conducted for Omnitrope as per ICHS6.

Reproductive Toxicity: Nonclinical reproductive toxicity studies have not been conducted with Omnitrope.

Carcinogenicity: Carcinogenicity studies have not been conducted with Omnitrope.

3.4.7 Local Tolerance Study in New Zealand White Rabbits after IV, IM and SC Administration

Protocol#: [redacted] # 21/001-D
Study date: 9/7/2000-3/8/2001
Testing Facility: [redacted]

a. Objective:

The anticipated human therapeutic dose is 0.03 mg/kg/day. The sponsor wished to determine the potential local tolerability of the test article EP 2000 (Growth hormone formulations) following daily intravenous, intramuscular or subcutaneous administration of a higher dose (5 mg/day) in New Zealand White rabbit for 7 consecutive days under GLP conditions.

b. Methods:

Two formulations (Formulation I = Batch#S00200=rh-GH 5.8 mg and Formulation II = Batch#S0034360) were used in the following experimental design. Four male and four female rabbits/group received two formulations of Omnitrope and the vehicles daily for 7 days via im, iv or sc injections at the dose of 5mg/animal. The volume of injection was 1mL (lyophilized formulation) and 1.5mL (liquid formulation). Detailed clinical examinations of general health and of the injection sites were made every day; 2 animals/sex/group were killed on D8 (one day post-dosing) and the remaining two animals on D22 (2 weeks post-dosing).

Group number	Dosing formulation	Route of administration	Dose level (mg/animal/day)	Dose volume (ml/site/day)	Number of animals Day 8(1)	Day 22(2)
1	Lyophilisate formulation	Intravenous	5	1	4	4
2		Intramuscular	5	1	4	4
3		Subcutaneous	5	1	4	4
4	Liquid formulation	Intravenous	5	1.5	4	4
5		Intramuscular	5	1.5	4	4
6		Subcutaneous	5	1.5	4	4

(1) killed the day after the last administration (day 8).

(2) killed 2 weeks after the last administration (day 22).

Morbidity/mortality was examined at least twice daily. Clinical examinations were performed daily and injection sites were examined twice daily (before and 2 hours after administration) during the treatment period (days 1 to 7) then daily during the treatment-free period.

Individual body weights were recorded prior to dosing then twice weekly.

Half of the animals were killed at the end of the treatment period (day 8) and the remaining half of the animals at the end of the treatment-free period (day 22). Injection sites were fixed and preserved at necropsy for all animals. These tissues were examined histopathologically.

c. Results:

There were no unscheduled deaths and treatment-related effects on body weight were not evident.

There were signs of mechanical injection trauma in all groups including the control placebo groups. The liquid formulation and its vehicle were associated with slight erythema at the sites of the IV injections and with some local induration. The erythema had disappeared by about D13, i. e. 6 days after the last injection. The incidences were not frequent after administration of the products and erythema was not observed after D8.

No particular reaction was seen at the sites of the IM injections other than the effects of mechanical trauma of injection. The subcutaneous injection sites in all groups showed small hemorrhages attributed to mechanical trauma and minimal edema and erythema, slightly more marked after the lyophilized formulation, and some induration after the vehicle of that formulation.

Both formulations appear to have a slight local effect after intravenous or subcutaneous administrations, but not after repeated IM injections. There was no report of any indication of untoward local reaction at the sites of repeated subcutaneous injections.

Outline of the local tolerance study

Title	EP2000 (Growth hormone formulations) – Local tolerance in rabbits by intravenous, intramuscular and subcutaneous routes
Investigational product	Omnitrop 5.8 mg lyophilized powder [batch 6000140823 (S00200); diluent 907973] and Omnitrop liquid 5 mg/1.5 mL solution in a cartridge [batch 6000140900 (0034360)]
Route of administration	Intravenous, intramuscular and subcutaneous injections
Duration	7 days of treatment
Dosage	Omnitrop powder for solution for injection: 5 mg/animal/day in a volume of 1 mL.
	Omnitrop solution for injection: 5 mg/animal/day in a volume of 1.5 mL.
	Vehicle: 1 or 1.5 mL depending on the dosing formulation.
Test system	48 male New Zealand White rabbits were divided into 6 groups. The rabbits were randomized using random stratified body weight procedures.
Observations	Morbidity/mortality: All animals were observed at least twice daily.
	Clinical signs or reactions to treatment: All animals were examined twice daily during the treatment period.
	Injection sites: All animals were examined twice daily (before and at least 2 hours after administration) from day 1 to 7 and daily thereafter.
	Body weight was recorded twice weekly.
Pathology	Half of the animals were killed on day 8, and the remaining half of the animals on day 22. Necropsies were performed on all animals.
	The injection sites were sampled of all animals.

Unresolved toxicology issues (if any): None.

3.6 OVERALL CONCLUSIONS AND RECOMMENDATION:

Recombinant human growth hormones from various sources have been used for many years without significant adverse effects. Based on chemical identification of Omnitrope as hGH and the clinical efficacy and safety findings, pharmacology concludes that the drug product is safe for use.

Pharmacology Recommendations: None.

3.7. SUGGESTED LABELING:

Carcinogenicity, Mutagenicity, Impairment of Fertility:

Mutagenicity or carcinogenicity studies have not been conducted with Omnitrope.

Pregnancy: Pregnancy Category B
(Pregnancy labeling is identical to that for other FDA-approved GH products.)

Reproduction studies carried out with recombinant human growth hormone (rhGH) at doses of 0.3, 1, and 3.3 mg/kg/day administered SC in the rat and 0.08, 0.3, and 1.3 mg/kg/day administered intramuscularly in the rabbit (highest doses approximately 24 times and 19 times the recommended human therapeutic levels, respectively, based on body surface area) resulted in decreased maternal body weight gains but were not teratogenic. In rats receiving SC doses during gametogenesis and up to 7 days of pregnancy, 3.3 mg/kg/day (approximately 24 times human dose) produced anestrus or extended estrus cycles in females and fewer and less motile sperm in males. When given to pregnant female rats (days 1 to 7 of gestation) at 3.3 mg/kg/day a very slight increase in fetal deaths was observed. At 1 mg/kg/day (approximately seven times human dose) rats showed slightly extended estrus cycles, whereas at 0.3 mg/kg/day no effects were noted.

In perinatal and postnatal studies in rats, rh-GH doses of 0.3, 1, and 3.3 mg/kg/day produced growth-promoting effects in the dams but not in the fetuses. Young rats at the highest dose showed increased weight gain during suckling but the effect was not apparent by 10 weeks of age. No adverse effects were observed on gestation, morphogenesis, parturition, lactation, postnatal development, or reproductive capacity of the offsprings due to rh-GH. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing mother:

There have been no studies conducted with rh-GH in nursing mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when rh-GH is administered to a nursing woman.

3.8. Appendix 1- review for IND58,980.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

KEY WORDS: Growth Hormone; hGH, EP2000
Reviewer Name: David H. Hertig
Division Name: DMEDP
HFD#: 510
Review Completion Date: 23 Aug 00
Electronic file number:
IND number: 58,980
Serial number/date/type of submission: SN-000 and SN-007
Information to sponsor: Yes ( ) No (X)
Sponsor: Biochemi GmbH, Biochemistrasse 10, 6250 Kundl/Austria
Agent: Nagesh Plaepu, Ph.D., Geneve Pharmaceuticals, Inc. (Novartis AG subsidiary)
Manufacturer of drug substance: Covance Biotechnology Services, North Carolina. Drug Product
was made at [redacted]
Drug:
Code Name: EP2000
Generic Name: Somatropin
Trade Name: BC rhGH, EP2000, Recombinant Human Growth Hormone, Somatropin, Somatotropin
Molecular Formula/ Molecular Weight: $C_{990}H_{1528}N_{262}O_{300}S_7$ 191 amino acids with a sequence identical to that of natural pituitary hGH. The protein molecule contains 4 cysteins, which form 2 intramolecular disulfide bonds between positions Cys 53-Cys 165 and Cys 182-Cys 189. MW [redacted] daltons. The isoelectric point is at pH 5.1.
Relevant INDs/NDAs/DMFs: Genotropin, NDA 20-280
Drug Class: Human Growth Hormone
Indication: Growth retardation in pituitary GH-deficient children.
Clinical formulation: The EP2000 (5.8 mg form) final product intended for marketing is supplied as a
sterile, white, lyophilized power in vials containing 5.8 mg (17.4 IU) of active substance. It is provided with a vial containing the Diluent for EP2000 5.8 mg (water for injection with 1.5% benzyl alcohol as a preservative).
Excipients:
Glycine 27.6 mg
Sodium dihydrogen phosphate [redacted]
[redacted]
pH 7.1
Route of administration: subcutaneous
Proposed clinical protocol or Use:
Phase I safety study (completed): Six male and 6 female healthy volunteers received BC rhGH in a randomized, double-blind, placebo-controlled 2-way crossover study. Subjects received either a single s.c. bolus injection of BC rhGH (ca 5 mg) and after a one week wash-out single dose of Placebo (Water for Injection) or first a single dose of Placebo and then a single dose of BC rhGH. The study was aimed at assessing the safety and tolerance of BC rhGH and at validating the pK/PD model to be used in a subsequent Phase I comparative trial (bioequivalence study), in which BC rhGH is to be compared to another preparation of rhGH. Endogenous GH is suppressed by a continuous infusion of Octreotide.
Phase III: The dosage of EP2000 for the treatment of GH deficiency should be individualized and adapted to each patient. The recommended dose of EP2000 in growth hormone deficient children is 0.1 IU/kg (0.03 mg/kg) body weight/day. EP2000 should be administered daily as a s.c. injection; administration in the evening is recommended. The s.c. injection site should be alternated to prevent lipoatrophy.

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

Studies reviewed within this submission: A 14-Day Subcutaneous Study in Rats;
A Toxicokinetic Analysis of the 14-Day Rat Study.

TOXICOLOGY

Study Title: A 14-Day study with EP2000 Administered by Daily Subcutaneous Injection to Sprague-Dawley Rats
Study No: 981106
Amendment #, Vol. #, and page #: N-003; Vol. 2.1 page 00194
Conducting laboratory and location: [redacted]

Date of study initiation: 28 May 99; Report Date - 29 Nov 99.
GLP compliance: Yes
QA – Report Yes (X) No ( )
Methods:
Dosing: Sponsor's Table V2.1/000199 14 Day subcutaneous

Treatment Groups	Dose Level (mg/kg/day)	Dose Conc. (mg/mL)	Dose Volume (mL/kg)	Number of Animals	
				Males	Females
1 (Control)*	0	0	2	10	10
2	2	4	0.5	10	10
3	8	4	2	10	10

* Control animals received the vehicle only.

- **Species / strain:** Male and female Sprague-Dawley rats
- **Age:** 7-9 weeks old
- **Weight:** Males 285 to 324g ; Females 236 to 281g [slightly older and heavier than protocol]
- **Satellite groups used for toxicokinetics or recovery:** See Toxicokinetics – below.
- **Dosage groups in administered units:** 0 (vehicle), 2, 8 mg/kg/day for 14 days

Drug, lot #, radiolabel (if applicable), and % purity: Batch/Lot No. 3056-CV38V01; Purity [redacted]

Observation and times:
- **Clinical signs:** once daily pretreatment; twice daily during treatment
- **Body weights:** once prior to randomization; daily during treatment period
- **Food consumption:** weekly
- **Ophthalmoscopy:** prior to treatment and prior to necropsy.
- **Clinical chemistry:** at termination
- **Hematology:** at termination
- **Urinalysis:** at termination
- **Organ Weights:** at termination
- **Gross pathology:** at termination
- **Organs weighed:** See Histology Table below p. 5.
- **Histopathology:** See Table below p. 5 .
- **Toxicokinetics:** See below p. 6.

2 rats/sex/group were sampled for blood (for pharmacokinetic analysis) on three occasions (Days 1, 7 and 14 at each of the following time-points: 0(pre-dose), 2, 4, 6 and 10 hours post-dose.

Results:

- **Mortality**: None drug related. [One group 3 (high dose male) died during blood collection.]
- **Clinical signs:** No signs of ill health. Two males on 2 mg/kg experienced respiratory distress (gasping) 10-15 min after dosing on day 9. One female from the 2 mg/kg observed to be gasping on the morning of Day 9.
- **Body Weights:** [Group means at 0, 2, 8 mg/kg (SD)]
  Body weight gain of males similar in all groups, however, high dose group mean body weights were consistently greater than that of corresponding controls [332 (26.7), 334 (31.7), 346 (20.8) g].
  Treated females increased in a dose dependent manner as of Day 2. [Final: 245 (15.7), 269 (14.0), 285 (19.0) g.]

- **Food Consumption:** 8 mg/kg Females ate slightly more than controls (Week 1: 181g vs 164g; Week 2: 171g vs 154 g).
  2 mg/kg females and treated males were similar to controls.
- **Ophthalmoscopy:** No apparent treatment related changes.

- **Hematology**: No apparent toxicologically significant differences from controls. However, mean white blood cell counts were higher than controls in both males (10.0 vs 8.7 x 10^9/L) and females (7.5 vs 6.9 x 10^9/L) on 2 mg/kg. Concurrent (control, low,hd) slight increases in mean neutrophil (0.88, 1.66, 1.21 x 10^9/L), monocyte (0.88, 1.66, 1.21 x 10^9/L), eosinophil (0.09, 0.16, 0.12 x 10^9/L) and basophil (0.08, 0.12, 0.11 x 10^9/L) counts were seen in 2 and 8 mg/kg males. Only mean neutrophil (0.93, 1.17, 1.06 x 10^9/L) and eosinophil (0.11, 0.14, 0.10 x 10^9/L) counts appeared to show slight increases in females. At 2 and 8 mg/kg both mean monocyte (0.28, 0.24, 0.19 x 10^9/L) and basophil (0.14, 0.13, 0.08 x 10^9/L) counts showed a decrease in females. These changes appeared to be minor in nature without a clear dose relationship. Coagulation showed no significant differences from controls.

- **Clinical Chemistry:** [Group means at 0, 2, 8 mg/kg (SD)]
  Males:
  AST - slight decrease in 8 mg/kg males compared to controls. [114 (36.2), 112 (41.7), 91 (18.5) IU/L]
  Females:
  AST - decreased in both groups [141 (38.8), 116 (38.0), 102 (23.8) IU/L]
  ALP - dose dependent increase in both groups [75 (21.2), 96 (27.5), 130 (36.8) IU/L]
  ALT - decrease in both groups [57 (30.6), 29 (9.0), 28 (5.2) IU/L]
  PROT - group mean total protein slightly decreased [68 (5.5), 63 (3.1), 62 (2.5) g/L]
  ALB – decreased [49 (4.0), 43 (1.5), 42 (2.2) g/L]
  A/G - decreased. [2.46 (0.292), 2.26 (0.195), 2.13 (0.277)]
  TRIG - slight decrease [0.27 (0.144), 0.15 (0.043), 0.19 (0.047) mmol/L]
  CRE (Creatinine) - decrease at 2 mg/kg [31 (5.3), 22 (3.3), 26 (3.8) µmol/L]

- **Urinalysis:** Comparable with controls.
- **Organ Weights:** [Group means at 0, 2, 8 mg/kg (SD)]
  Males:
  Not significantly affected.
  Females: No correlation with histopathological findings.
  Spleen – relative weights increased.
  [0.208 (0.0265), 0.240 (0.0318), 0.256 (0.0291)]
  Heart – relative weights decreased [0.406 (0.0203), 0.364 (0.0333), 0.361 (0.0215)].

Kidneys – relative weights (paired) decreased [0.683 (0.0458), 0.652 (0.0446), 0.633 (0.0350)].
Thymus – relative weights increased [0.116 (0.0246), 0.131 (0.0290), 0.149 (0.0331)].
Liver - slight increase relative high dose [2.866 (0.2311), 2.828 (0.1984), 2.974 (0.1839)].

- **Gross pathology:** No apparent drug related findings. At 2 mg/kg 5/10 males had a dark area and/or dark foci in the lungs. Dark areas in the lungs were also present in 3 males of the 8 mg/kg group.
- **Histopathology:** Various incidental changes (including inflammation and congestion) were seen, however, no apparent drug related histopathological changes were evident.
- **Toxicokinetics:** See TOXICOKINETICS section below p.6.

Overall Toxicology Summary:

EP2000 was administered at 0, 2 or 8 mg/kg subcutaneously for 14 consecutive days to 10/sex/group Sprague-Dawley rats. Blood samples were taken from two rats/sex/group on days 1, 7, and 14 for pharmacokinetic analysis. There was no apparent drug related signs of ill health or mortality. A dose related increase of group mean body weights was evident in females but not in males. There was a concurrent increase in mean food consumption for the high dose females. Mean food intakes for the low dose females and treated males were similar. The hematological profile of treated rats showed no apparent toxicologically significant differences. EP2000 did not significantly affect clinical chemistry of males. There were some changes in female blood chemistry parameters. These included decreases in AST, ALT, PROT, ALB, A/G ratio, TRIG and increases in ALP. According to the sponsor, these findings may have been due to metabolic effects of the drug. There was an absence of clear histopathological toxicological changes. The minor physiological or metabolic changes seen in females but not males were considered by the sponsor to be due to the smaller female size and lower growth rate. The validity of this reasoning is uncertain. Organ weights of female rats showed minimal increases in relative spleen weights and decreases in relative heart and kidney weights in both female treated groups. Macroscopic and microscopic findings appeared to be incidental to treatment.

Histopathology Inventory for IND

Study	981106			
Species	Rat			
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				
Gross lesions				
Harderian gland				
Heart	X*			
Hyphophysis				
Ileum	X			
Injection site				
Jejunum	X			
Kidneys	X*			
Lachrymal gland				
Larynx				
Liver	X*			
Lungs	X			
Lymph nodes, cervical				
Lymph nodes mandibular	X			
Lymph nodes, mesenteric	X			
Mammary Gland	X			
Nasal cavity				
Optic nerves	X			
Ovaries	X*			
Pancreas	X			
Parathyroid	X*			
Peripheral nerve				
Pharynx				
Pituitary	X*			
Prostate	X			
Rectum				
Salivary gland	X			
Sciatic nerve	X			
Seminal vesicles	X			
Skeletal muscle	X			
Skin	X			
Spinal cord	X			
Spleen	X*			
Sternum	X			
Stomach	X			
Testes	X*			
Thymus	X*			
Thyroid	X*			
Tongue	X			
Trachea	X			
Urinary bladder	X			
Uterus	X			
Vagina	X			
Zymbal gland				

* organ weight obtained.

PHARMACOKINETICS/TOXICOKINETICS

IND 58,980 SN-007 dtd. 19 July 2000 Vol. 6.3/000753 Final Version dtd. 19 Jan 2000
Includes:
Toxicokinetic analysis of the 14-day Rat Toxicology study above.
[redacted], performed the Toxicokinetic data analysis.

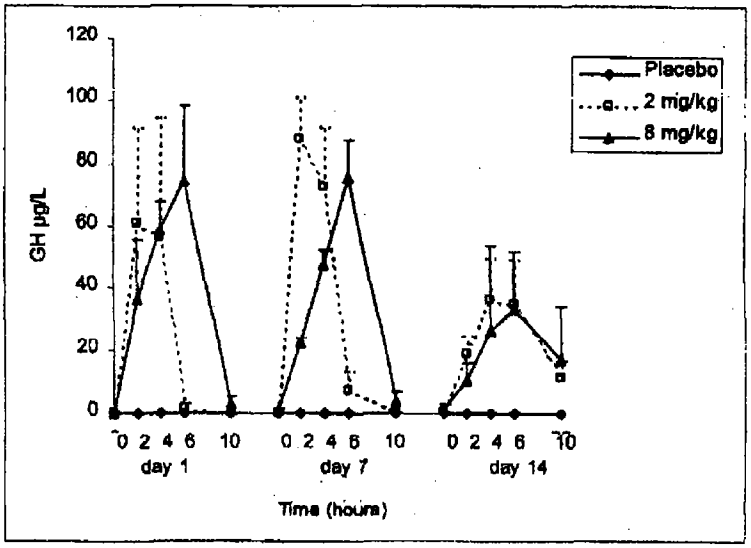
Dose levels: 0, 2 and 8 mg/kg EP2000.

Blood samples for the determination of GH levels were collected from 2 rats of each sex at the following time-points: 0 (pre-dose), 2, 4, 6 and 10 hours after s.c. administration of EP2000 on Days 1, 7 and 14.

See Tables below and Comments/Summary p. 12.

Sponsor's Figure: Vol. 6.3/000759

Figure 2: Mean (± SD) GH levels after repeated (every 24 hours during 14 days) s.c. administration of placebo, EP2000 2 mg/kg and EP2000 8 mg/kg



Sponsor's Table: Vol. 6.3/000760

Table 4: C_{max}, T_{max}, and AUC_{last} on days 1, 7 and 14 after repeated s.c. administrations of EP2000 2 mg/kg and 8 mg/kg every 24 hours in rats.

Rat ID #	2501	2506	2006	2001	Mean	SD	3506	3501	3106	3001	Mean	SD	*Ratio of mean 8 / 2 mg/kg*
Sex	F	F	M	M			F	F	M	M			
Dose (mg/kg)	2	2	2	2			8	8	8	8			*4*
Day 1													
C_{max} (µg/L)	20.3	88.7	66.5	78.5	63.5	30.2	57.9	98.4	71.1	85.3	78.2	17.5	*1.2*
T_{max} (h)	2	2	4	2	2.5	1.0	4	6	6	6	5.5	1.0	*2.2*
AUC_{last} (h·µg/L)	41	350	258	308	240	137	295	499	456	426	419	88	*1.7*
Normalized AUC_{last} (h·µg/L·kg)	166	1274	891	1074	851	483	1176	1995	1442	1374	1497	351	*1.8*
Day 7													
C_{max} (µg/L)	94.6	107.5	86.0	78.8	91.7	12.3	71.3	78.2	90.0	61.5	75.3	12.0	*0.8*
T_{max} (h)	4	2	2	2	2.5	1.0	6	6	6	6	6.0	0.0	*2.4*
AUC_{last} (h·µg/L)	395	319	334	322	342	36	347	388	432	329	374	46	*1.1*
Normalized AUC_{last} (h·µg/L·kg)	1489	1071	1091	1030	1171	214	1249	1427	1233	967	1219	190	*1.0*
Day 14													
C_{max} (µg/L)	22.4	43.7	38.9	50.9	39.0	12.1	9.0	43.0	66.5	41.9	40.1	23.6	*1.0*
T_{max} (h)	6	4	4	6	5.0	1.2	6	6	4	10	6.5	2.5	*1.3*
AUC_{last} (h·µg/L)	156	273	209	316	239	70	65	219	329	218	208	108	*0.9*
Normalized AUC_{last} (h·µg/L·kg)	562	833	634	948	744	178	224	734	864	575	599	277	*0.8*

Sponsor's Table: Vol. 6.3/00761

Table 5: Ratios of C_{max}, T_{max}, and AUC_{last} on days 7 and 14 versus day 1 after repeated s.c. administration of EP2000 2 mg/kg and 8 mg/kg every 24 hours in rats.

Rat ID #	2501	2506	2006	2001	Mean	SD	3506	3501	3106	3001	Mean	SD
Sex	F	F	M	M			F	F	M	M		
Dose (mg/kg)	2	2	2	2			8	8	8	8		
Ratio day 7/ day 1												
C_{max} (µg/L)	*4.7*	*1.2*	*1.3*	*1.0*	*2.0*	*1.7*	*1.2*	*0.8*	*1.3*	*0.7*	*1.0*	*0.3*
T_{max} (h)	*2.0*	*1.0*	*0.5*	*1.0*	*1.1*	*0.6*	*1.5*	*1.0*	*1.0*	*1.0*	*1.1*	*0.3*
AUC_{last} (h·µg/L)	*9.6*	*0.9*	*1.3*	*1.0*	*3.2*	*4.2*	*1.2*	*0.8*	*0.9*	*0.8*	*0.9*	*0.2*
Ratio day 14/ day 1												
C_{max} (µg/L)	*1.1*	*0.5*	*0.6*	*0.6*	*0.7*	*0.3*	*0.2*	*0.4*	*0.9*	*0.5*	*0.5*	*0.3*
T_{max} (h)	*3.0*	*2.0*	*1.0*	*3.0*	*2.3*	*1.0*	*1.5*	*1.0*	*0.7*	*1.7*	*1.2*	*0.5*
AUC_{last} (h·µg/L)	*3.8*	*0.8*	*0.8*	*1.0*	*1.6*	*1.5*	*0.2*	*0.4*	*0.7*	*0.5*	*0.5*	*0.2*

Sponsor's Table: Vol. 6.3/000761

Table 6: Comparison of C_{max}, T_{max} and AUC_{last} (ratios of the individual parameters) between genders

Ratio Female/Male	2 mg/kg	8 mg/kg
Day 1		
C_{max} (µg/L)	0.8	1.0
T_{max} (h)	0.7	0.8
AUC_{last} (h·µg/L)	0.7	0.9
Day 7		
C_{max} (µg/L)	1.2	1.0
T_{max} (h)	1.5	1.0
AUC_{last} (h·µg/L)	1.1	1.0
Day 14		
C_{max} (µg/L)	0.7	0.5
T_{max} (h)	1.0	0.9
AUC_{last} (h·µg/L)	0.8	0.5

PHARMACOKINETICS/TOXICOKINETICS Comments and Summary:

Blood was collected from 2 rats/sex/treatment group (0, 2, 8 mg/kg EP2000) at 5 time- points (0, 2, 4, 6 and 10 h) on Days 1, 7, and 14. The same rats were sampled for each time point and for each day of EP2000 administration. The two doses were not administered to the same rats which confounds comparison between the two doses. Growth hormone (GH) levels below 0.1 µg/L were considered 0 µg./L.

GH levels were slightly higher at baseline on Day 14 before the administration of EP2000 2 mg/kg, and on Days 7 and 14 before the s.c. administration of 8 mg/kg EP2000. Thus, a slight accumulation of GH is suggested following repeated s.c. administration of EP2000 q 24 h. Accumulation is also suggested since GH levels did not return to baseline levels 10 hours after administration of 2 mg/kg on Day 14 and for the 8 mg/kg dose on Days 1, 7 and 14. The last measured GH levels at 10 hours after administration were markedly higher on Day 14 than on Day 1 or Day 7.

Sponsor's Table 4 shows mean maximal levels of GH (C_{max}) per dose level and per day of administration to be between 39.0 and 91.7 µg/L; the mean T_{max} ranged from 2.5 to 6.5 hours. Mean areas under the concentration-time curve (AUC_{last}) were between 208 and 419 h·µg/L. GH levels did not show a linear increase form 2-8 mg/kg. Ratios of the mean C_{max} and AUC_{last} were close to 1. [AUC was not extrapolated to infinity but to the last dose.]

According to the sponsor, the true C_{max} may have been missed due to the small number of data points that could also have influenced the AUC_{last}. They also stressed that the two doses were not administered to the same rats. The extent of these effects is uncertain.

Growth hormone release profiles and C_{max} and AUC_{last} show that on Day 14 GH release is slower than on Days 1 and 7. The C_{max} is smaller and the period of release is longer. [One aberrant rat in group 2 (# 2501) had low GH levels on Day 1 and Day 14 but not on Day 7. The T_{max} for this animal was also somewhat delayed on day 14.]

Although gender appeared to have no effect on the pharmacokinetics of the drug, only a small number of animals per sex/dose were used in this study. Findings for Days 1 and 14 of the 2 mg/kg group are of little use for determination of the influence of gender due to the variable GH exposure of female rat # 2501. C_{max}, T_{max} , and AUC_{last} for the 8 mg/kg dose are comparable on Day 1. Day 7 C_{max} , T_{max} , and AUC_{last} are generally comparable for both doses in both sexes.

OVERALL SUMMARY AND EVALUATION

Recombinant human growth hormone rhGH -- EP2000 is chemically identical to pituitary growth hormone (somatropin). EP2000, a non-glycosylated protein, is produced by recombinant DNA technology using a genetically modified strain of Escherichia coli K12. EP2000 (MW: daltons) is composed of 191 amino acids and has an amino acid sequence identical to that of the natural pituitary hGH.

It is reported that Genotropin, one of the first rhGHs to be registered in the US, is the closest comparator of EP2000 in terms of product identity, since it is produced using the same strain of E. coli as that used for EP2000 production. Genotropin is currently administered for the treatment of pituitary deficiencies and growth failure in children. Genotropin is also indicated for long-term replacement therapy in adults with GHD of either childhood or adult-onset etiology. For pediatric GHD patients generally, a dose of 0.16 to 0.24 mg/kg body weight/week is recommended.

Somatropin or EP2000 was reported to have been administered subcutaneously b.i.d. for 4 days for a total of 8 doses to male hypophysectomized Wistar rats (5 or 6/group), at doses of 0.06 or 0.12 IU/animal. The end-point was the change in body weight over the dosing period (Day 1 to Day 5). The increase in bodyweight produced by EP2000 appeared to be at least as potent as that produced by somatropin.

IND 58,980 p. 10

Safety of EP2000 has been evaluated in a 14-day repeated-dose toxicity study in rats with toxicokinetic analysis. Subcutaneous doses were 2 and 8 mg/kg. Slight effects were noted in some hematological and clinical chemistry parameters. In the absence of histopathological evidence of toxic changes, the minor changes seen in mainly female animals would appear to be a pharmacological response. With regard to safety, these parameters are easily monitored clinically.
[Note: Although the hematological and clinical chemistry findings were not the same as those found with Genotropin (NDA 20-280) the two rat studies were not completely analogous. The Genotropin study was of longer duration (1 month) and by a different route (i.m.) with lower doses (0.125, 0.625 and 3.125 mg/kg).]

A slight accumulation was seen in the toxicokinetic study. The increase between 2 and 8 mg/kg was not linear. Toxicokinetics of this GH did not show a sex difference following repeat doses of EP2000. The AUC was given only to the last dose and not extrapolated to infinity. There were only two rats/sex/dose level and the two doses were not administered to the same rats thus somewhat compromising appropriate comparisons of the two doses.

Clinically safety and tolerance have been assessed after a single administration in a Phase I safety study in healthy volunteers. According to the sponsor, pharmacokinetic and pharmacodynamic properties (similar to that of Genotropin) were demonstrated in the Phase I comparative study in healthy volunteers. Clinical safety, efficacy and therapeutic equivalence to Genotropin were reported to have been assessed in an open comparative Phase III study in GH-deficient children.

Although possible, development of neutralizing antibodies would be unexpected.

The sponsor appears to be pursuing a 505 (b)(2) application for this product.

Recommendation: AP
From the standpoint of Pharmacology, clinical trials may proceed.

David H. Hertig
Pharmacologist

cc: Original IND 58,980; HFD-510 Division File; HFD-345;
HFD-510 JElHage, DHertig, CKing
Recommendation: AP

The Toxicokinetic Report can be found in Appendix E.

Plasma concentration data as well as the toxicokinetic parameters (AUC_{0-t} and Cmax) obtained from male and female rats which received PAR NCD Megestrol Acetate were greater than those obtained from animals dosed with Megace at all dose levels and for each dosing day (Days 1, 30 and 90).

Gender differences were observed in the toxicokinetic profile of both Megace and PAR NCD Megestrol Acetate in Sprague-Dawley rats. The mean AUC_{0-t} and C_{max} for both test articles (Megace and PAR NCD Megestrol Acetate) were greater in female rats compared to male rats at almost each dose level and each dosing day (Days 1, 30 and 90). The difference between genders was more obvious at the lower doses.

At the lowest dose, the extent of absorption (AUC_{0-t}) was similar between Megace and PAR NCD Megestrol Acetate on each dosing day in both genders and was greater after multiple oral administrations (Days 30 and 90) compared to a single oral administration (Day 1). For the middle and the highest dose, there was a difference between both products regarding AUC_{0-t}; the extent of absorption was higher for PAR NCD Megestrol Acetate comparatively to Megace on all dosing days in both genders.

With regards to linearity, the female rats demonstrated the same profile for both products. In general, the toxicokinetic parameters (AUC_{0-t} and C_{max}) increased in a less than linear manner between 13.3 and 40.0 mg/kg/day but tended to plateau between 40.0 and 66.5 mg/kg/day. For male rats dosed with different concentrations of Megace, the mean AUC_{0-t} and Cmax increased linearly with the dose over dosing days (Days 1, 30 and 90) while for PAR NCD Megestrol Acetate administration, AUC_{0-t} and Cmax increased in greater than linear manner in male rats over dosing ranges on almost all dosing days.

13.8. Pathology Results

Details can be found in the Pathology Report, Appendix F.

13.8.1. Gross Pathology, Terminal Body Weights, and Organ Weights

Gross examination demonstrated prominent decrease in the size of the adrenal glands, which was confirmed by the decreased organ weights, in all doses in both sexes receiving Megace. In males there was decreased size of testes, epididymides, and secondary sex glands (prostate and seminal vesicle) principally in the 40 and 66.5 mg/kg groups but in a few animals at the 13.3 mg/kg dose level.

With NCD there was similar reduction in adrenal gland size in all doses and in both sexes. In males there was reduced size of the reproductive tissues (as in Megace) with incidence related to dose. Additionally, in females there was a non-dose-related decrease in the size of the ovary at all doses.

Terminal Body and Organ Weights

Megace Males

At the regular group termination there was a statistically significant decrease in terminal body weight at the 40 and 66.5 mg/kg dose. There was a statistically significant decrease in absolute and relative adrenal weights at all doses. Absolute and relative spleen and prostate weights were decreased at all doses with testes weights decreased at 40 and 66.5 mg/kg. Additionally, there were statistically decreased absolute brain and lung weights at 66.5 mg/kg and decreased heart and kidney weights at 40 and 66.5 mg/kg Megace. Relative organ weights also noted as statistically decreased were thymus and liver at 66.5 mg/kg and kidney at both the 13.3 and 6.5 mg/kg dose.

In the recovery group males, there was a statistically significant decrease in terminal body weights with statistically decreased adrenal, heart, kidney, liver, testes and pituitary. The absolute thymus weights were statistically increased. Relative brain, thymus, and spleen weights were statistically increased and relative pituitary weights were decreased.

Megace Females

The regular group termination was characterized by extensive organ weight changes as in males. There were decreased absolute and relative adrenal, ovary, spleen, and uterus weights at all doses. Additionally, absolute and relative brain weights were statistically decreased at 40 and 66.5 mg/kg Megace with liver weights increased at 66.5 mg/kg (note decreased relative liver weight at 13.3 mg/kg). The liver weight changes are more likely to be related to the corresponding group terminal body weights rather than other biological events. There were statistically decreased absolute and relative pituitary weights at 66.5 mg/kg (with relative decrease at 40 mg/kg).

Recovery group 66.5 mg/kg females had a slight non-statistical increase in terminal body weights with corresponding statistical increases in absolute and relative spleen and thymus weights. There were statistically decreased absolute pituitary weights (non-statistical relative weight decrease) and statistically decreased relative uterine weights (non-statistical absolute uterine weight decrease).

NCD Males

There was a statistical and dose-related decrease in terminal body weight in the 40 and 66.5 mg/kg regular group NCD males. Statistically significant decrease in absolute and

relative adrenal, spleen, prostate, and absolute kidney weights were seen at all doses. Additionally, there were statistically decreased absolute brain and heart weights at 40 and 66.5 mg/kg and lung and pituitary weights at 66.5 mg/kg. Absolute testes weights were statistically decreased at all doses with statistically significant relative weight decreases at 40 and 66.5 mg/kg. Relative thymus weights were statistically increased at 40 and 66.5 mg/kg with relative liver weight increased at 66.5 mg/kg.

Recovery group 66.5 mg/kg NCD males had statistically decreased terminal body weights with statistically decrease absolute adrenal, heart, kidney, testes, and pituitary weights. There were statistically significant increased absolute and relative thymus weights and increased relative brain and spleen weights. All of these weight changes were interpreted to be a reflection of the lower terminal body weights in this group.

NCD Females

There were no statistical differences in terminal body weights from the control group in the regular group NCD females. There were statistically decreased absolute and relative adrenal, ovary, and uterine weights at all doses. In addition, there were statistically decreased absolute and relative brain weights at 13.3 and 66.5 mg/kg NCD. Absolute spleen weight decrease at 66.5 mg/kg was associated with relative spleen weight decrease at all doses. There was an absolute and relative increase in liver weights at 66.5 mg/kg (relative decrease at 13.3 mg/kg). Relative lung weights were also statistically decrease at 40 and 66.5 mg/kg. There was a statistical non-dose-related decrease in relative pituitary weights at 13.3 and 66.5 mg/kg NCD and absolute pituitary weight decrease at 13.3 mg/kg.

The recovery group 66.5 mg/kg NCD had similar terminal body weight as the concurrent control group. There was a slight but statistical decrease in absolute and relative pituitary weights. The relative thymic weight was statistically increased.

Overall, there were significant organ weight changes generally associated with significant terminal body weight changes in both sexes with both Megace and NCD in this study. The extent of weight change was generally dose-related. There was no no-observed-effect level (NOEL) related to organ weights.

13.8.2. Clinical Pathology

There were notable statistically altered clinical chemistry and hematology parameter changes in both sexes in Megace and NCD Megestrol. These changes were most often in the 40 and 66.5mg/kg dose groups in a dose-related fashion.

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/s/

Herman Rhee
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2/16/05 12:39:05 PM
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45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

NDA No. 21-426/Biochemie/Omnitrope(rh Growth Hormone)/A [redacted]

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? **Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA** (None)	X		Have electronic files of the carcinogenicity studies been submitted for statistical review? N/A **Studies completed:** 1) 14-Day tox study in rat(981106) 2) Local tolerance study in rabbits for 7 days after im/iv/sc administration 3) No carcinogenity study 4) No genotoxicity studies (Cited data for Genotropin and other GH) 5) No reproductive studies (Cited data for Genotropin and other GH) 6) Four 10-day studies comparing 6 different formulations of human GH

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	X		
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	X		
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	X		

8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	X		

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	X		
10) Reasons for refusal to file:			

Herman Rhee, Ph.D.
Reviewing Pharmacologist

Jeri Elhage, Ph.D.

Supervisory Pharmacologist

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

/s/

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