CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-426

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-426	Submission Date: 08/08/2003, 04/02/2004
Brand Name	Omnitrope™
Generic Name	Somatropin [rDNA origin] for injection
Reviewer	Xiaoxiong (Jim) Wei, M.D., Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM division	Division of Endocrine and Metabolic Drug Products (HFD-510)
Sponsor	Biochemie
Relevant IND(s)	58,980
Submission Type; Code	Original
Formulation; Strength(s)	1.5 mg and 5.8 mg lyophilized powder
Dosing regimen	The dosage is adjusted for the individual patient. Daily administration by subcutaneous injection in the evening is recommended. Pediatric GHD patients: Generally, a dose of 0.16 to 0.24 mg/kg body weight/week; Adult HGD patients: 0.04 – 0.08 mg/kg body weight/week.
Indication	(1) Long-term treatment of pediatric patients with growth hormone deficiency (GHD) (2) Long-term replacement therapy in adults with growth hormone deficiency (GHD) of either childhood- or adult- onset etiology.

Table of Contents

1. EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS

From the Clinical Pharmacology and Biopharmaceutics standpoint, the application is acceptable for Omnitrope 5.8 mg lyophilized powder. A bioequivalence waive request for Omnitrope 1.5 mg lyophilized powder can not be granted because the composition of 1.5 mg formulation is not proportional to 5.8 mg formulation. This recommendation should be conveyed to the sponsor as appropriate.

1.2 Phase IV

Not applicable

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

OMNITROPE™ Lyophilized Powder contains somatropin [rDNA origin, human growth hormone, hGH]. The amino acid sequence of OMNITROPE™ is identical to that of human growth hormone of pituitary origin (somatropin). OMNITROPE™ is a sterile white lyophilized powder intended for subcutaneous injection. Omnitrope is proposed for indications for (1) long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone; (2) long-term replacement therapy in adults with growth hormone deficiency (GHD) of either childhood- or adult- onset etiology. The NDA submission also includes a comparative study between Omnitrope and Genotropin®. The sponsor has conducted and submitted pivotal clinical trials in pediatric patients with GHD.

All human studies in clinical pharmacology and biopharmaceutics were performed in healthy adults. In a placebo-controlled, two-way cross-over study, 12 healthy male and female subjects received subcutaneous bolus injection of 5 mg of Omnitrope or placebo. The endogenous growth hormone (GH) was completely suppressed by a continuous infusion of octreotide at a rate of 0.04 mg/h over 25 hours (-1 to 24 hours), which provides a model system for bioequivalence study of human growth hormone to be conducted in healthy subjects without interference of endogenous growth hormone. This single dose administration of Omnitrope also induced significant increases in IGF-1 and IGFBP-3 serum levels when compared to placebo.

Because a liquid formulation was used in the latest stage of phase 3 pivotal clinical trials and all other formulations were lyophilized powders including the to-be-marketed formulation, the sponsor conducted a 2-way cross-over study to assess the bioequivalence between Omnitrope (lyophilized powder formulation) and Omnitrope^{AQ} (liquid formulation) in 24 healthy volunteers after a single subcutaneous bolus injection

of 5 mg Omnitrope. The pharmacodynamic response to Omnitrope^{AQ} and Omnitrope was also assessed by Cmax and $AUC_{0\text{-last}}$ of the serum concentrations of IGF-1 and IGFBP-3 (up to 96 hours post-dose). The results have showed that 90% confidence intervals for both Omnitrope PK and PD parameters (AUC and Cmax) were lying within the 80-125% bioequivalence range.

In a two-way cross-over study, the sponsor has compared the pharmacokinetics, pharmacodynamics of Omnitrope lyophilized powder (test drug product) with that of Genotropin® (reference drug product) in 24 healthy male and female subjects after a single subcutaneous bolus injection of either 5 mg of Omnitrope or 5 mg of Genotropin®. 90% confidence intervals for both pharmacokinetic and pharmacodynamic parameters (Cmax and AUC) were maintained within 80-125% range.

The sponsor has developed two strength formulations for marketing, 5.8 mg and 1.5 mg lyophilized powder. The Omnitrope 1.5 mg lyophilized powder formulation has not been tested in any clinical trials. The composition of 1.5 mg lyophilized powder formulation is not proportional to that of the 5.8 mg lyophilized powder formulation. Therefore, the sponsor's request for a waiver for a BE study for 1.5 mg lyophilized powder formulation can not be granted.

The to-be-marked formulation of 5.8 mg lyophilized powder has been slightly modified from the phase 3 formulation, changing [redacted] in the to-be-marketed formulation. The final pH of 7.0 remains the same.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulations of the drug product?

OMNITROPE™ Lyophilized Powder contains somatropin [rDNA origin, human growth hormone], which is a polypeptide hormone of recombinant DNA origin. It has 191 amino acid residues and a molecular weight of [redacted] Daltons. The amino acid sequence of the product is identical to that of human growth hormone of pituitary origin (somatropin). OMNITROPE™ is synthesized in a strain of *Escherichia coli* that has been modified by the addition of the gene for human growth hormone. OMNITROPE™ is a sterile white lyophilized powder intended for subcutaneous injection.

2.1.2 What is the mechanism of action, therapeutic indication and dosage recommendations for Omnitrope?

Mechanism of Action

Somatropin (human Growth Hormone, hGH) exerts many of its physiological functions by regulating the transcription of genes for a variety of proteins, including insulin-like growth factor-1 (IGF-1), transcription factors and metabolic enzymes. IGF-1 can act either locally or systemically. There are six known IGF-1 binding proteins (IGFBPs 1-6) which have a strong affinity to IGF-1. The binding proteins play important regulatory roles in controlling the bioavailability and action of IGF-1. About 90% of IGF-1 is bound to IGFBP-3. Together with the acid-labile sub-unit (ALS), IGF-1 and IGFBP-3 form a stabile ternary 150 kDa complex, which is of importance for IGF-1 bioactivity. This complex extends the half-life of IGF-1 to 12-14 h, compared with approximately 10 min when free, and thereby facilitates its endocrine effects.

In pediatric patients who have growth hormone deficiency (GHD), treatment with somatropin stimulates linear growth and normalizes concentrations of IGF-I. In adults with GHD, treatment with somatropin results in reduced fat mass, increased lean body mass, metabolic alterations that include beneficial changes in lipid metabolism, and normalization of IGF-I concentrations.

In vitro, preclinical and clinical tests have demonstrated that OMNITROPE™ Lyophilized Powder is equivalent to human growth hormone of pituitary origin.

Proposed Indications

OMNITROPE™ Lyophilized Powder is indicated for (1) long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone; (2) long-term replacement therapy in adults with growth hormone deficiency (GHD) of either childhood- or adult- onset etiology.

Proposed Dosage Recommendation

The dosage of OMNITROPE™ Lyophilized Powder must be adjusted for the individual patient. Daily administration by subcutaneous injection in the evening is recommended. OMNITROPE™ may be given in the thigh, buttocks, or abdomen; the site of SC injections should be rotated daily to help prevent lipoatrophy. For pediatric GHD patients, generally, a dose of 0.16 to 0.24 mg/kg body weight/week is recommended. For adult GHD patients, the recommended dosage at the start of therapy is not more than 0.04 mg/kg/week. The dose may be increased at 4 to 8 week intervals to a maximum of 0.08 mg/kg/week.

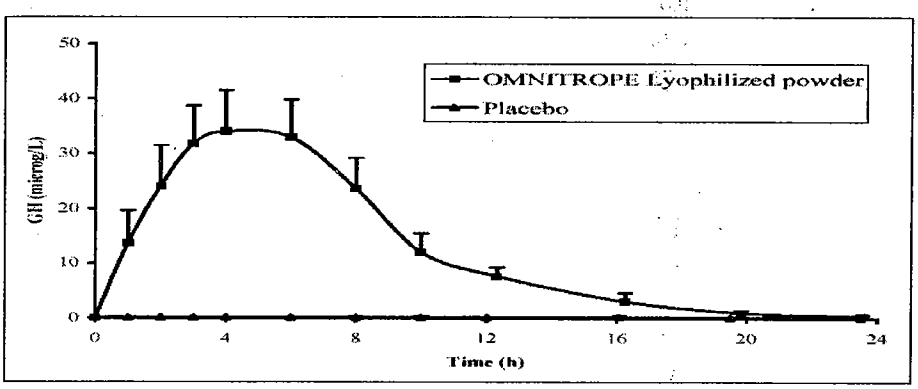
2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the pharmacokinetic and pharmacodynamic profiles of Omnitrope following a single subcutaneous administration in healthy subjects?

In a double-blind, randomized, placebo-controlled, two-way cross-over study to assess the safety, tolerance, pharmacokinetics and pharmacodynamics of Omnitrope, 12

healthy male and female subjects received subcutaneous bolus injection of 5 mg of Omnitrope or placebo. To accurately assess the pharmacokinetics of Omnitrope, endogenous growth hormone (GH) was suppressed by a continuous infusion of octreotide at a rate of 0.04 mg/h over 25 hours (-1 to 24 hours). The undetectable concentrations of endogenous human growth hormone (hGH) in placebo control arm have confirmed that the continuous iv infusion of octreotide is effective in completely suppressing endogenous hGH secretion in healthy human volunteers (Figure 1), which provides a model system for subsequent bioequivalence study of human growth hormone to be conducted in healthy subjects without interference of endogenous growth hormone.

Figure 1. The time-concentration profiles of Omnitrope and placebo control during continuous iv infusion of octreotide in healthy human subjects.



The pharmacokinetic parameters are summarized in the following table:

Table 1. PK parameters of Omnitrope following 5 mg bolus subcutaneous injection.

	C_{max} (µg/L)	t_{max} (h)	AUC_{inf} (h. µg/L)	ka	$t_{1/2}$	CL/F
Mean ± SD	**37 ± 9**	**3.6 ± 0.5**	**291 ± 42**	**0.4 ± 0.2**	**2.4 ± 0.4**	**18 ± 3**
Median	**37**	**3.5**	**290**	**0.4**	**2.4**	**17**
Min	**21**	**2.9**	**206**	**0.3**	**1.6**	**14**
Max	**55**	**4.5**	**350**	**0.7**	**3.3**	**24**

This single subcutaneous administration of 5 mg of Omnitrope Lyophilized powder also induced significant increases in IGF-1 and IGFBP-3 serum levels when compared to placebo (Table 2 and Figure 2a and 2b).

Table 2: Pharmacodynamic response following sc bolus injection of 5 mg Omnitrope or placebo

Treatment		IGF-1			IGFBP-3		
		Cmax (µg/L)	AUC (µg/L•h)	tmax (h)	Cmax (mg/L)	AUC (mg/L•h)	tmax (h)
Omnitrope™	Mean ± SD	424 ± 163	31890 ± 11415	34 ± 15	5.0 ± 1.0	399 ± 71	43 ± 15
	Median	367	26912	36	5.0	386	48
	Min	256	20935	16	3.7	292	16
	Max	818	52946	48	6.6	498	71
Placebo	Mean ± SD	279 ± 107	21674 ± 8497	44 ± 40	4.2 ± 0.9	344 ± 68	39 ± 33
	Median	253	18506	32	3.9	316	24
	Min	144	11742	0	2.6	239	0
	Max	546	40945	97	5.5	457	96

Figure 2a: IGF-1 serum concentrations following subcutaneous injection of Omnitrope (EP2000) or placebo (mean ± SD, n = 12)

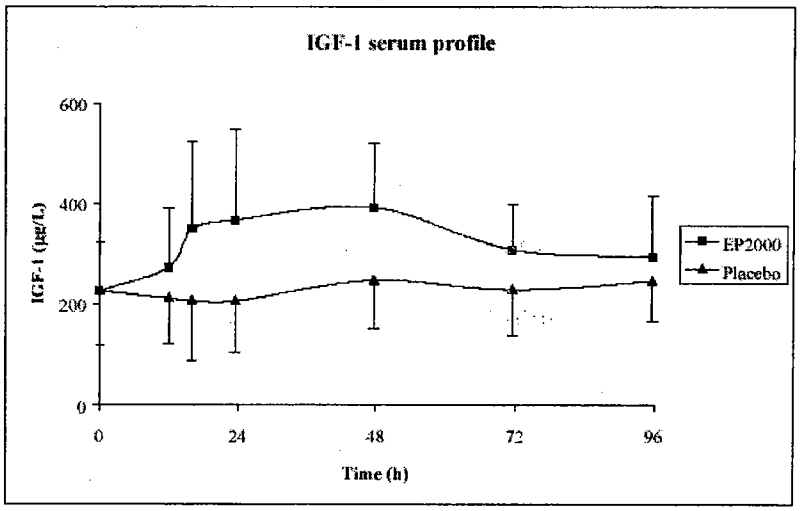
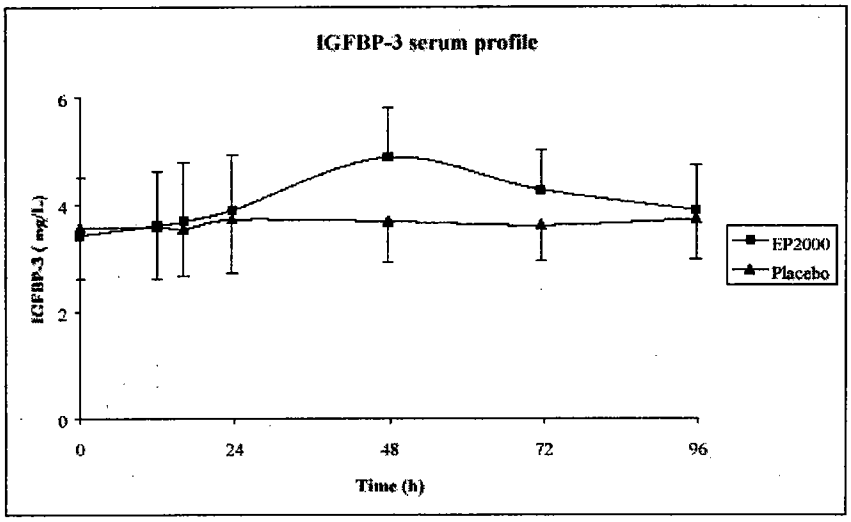


Figure 2b: IGFBP-3 serum concentrations following subcutaneous injection of Omnitrope (EP2000) or placebo (mean ± SD, n = 12)



From the PK profile above, the pharmacokinetics of Omnitrope is well described by a one-compartment model. The study also demonstrated that a single sc administration of 5 mg of OMNITROPE™ Lyophilized powder induced significant increases in IGF-1 and IGFBP-3, which returned to baseline within 96 h.

Reviewer's comment:

This study has demonstrated that the secretion of human growth hormone is suppressed completely by continuous intravenous administration of octreotide at a rate of 0.04 mg/hour, which simulates a condition of growth hormone deficiency. Therefore, a bioequivalence study conducted in such a setting would be similar to a BE study conducted in patients with growth hormone deficiency from the perspective of pharmacokinetics.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Is Omnitrope Liquid formulation bioequivalent to Omnitrope lyophilized powder formulation used in pivotal clinical trials?

Because a liquid formulation was used in the latest stage of phase 3 pivotal clinical trials and all other formulations including the to-be-marketed formulation were lyophilized powders, the sponsor conducted a double-blind, randomized, 2-way cross-over study to assess the bioequivalence between Omnitrope (lyophilized powder formulation) and Omnitrope^{AQ} (liquid formulation) in 24 healthy volunteers after a single subcutaneous bolus injection of 5 mg Omnitrope. The pharmacodynamic response to Omnitrope^{AQ} and Omnitrope was also assessed by Cmax, $AUC_{0\text{-last}}$ and tmax of the serum concentrations of IGF-1 and IGFBP-3 (up to 96 hours post-dose). Differences from baseline were calculated for Cmax and AUC0-last (Cmax and $AUC_{0\text{-last}}$,

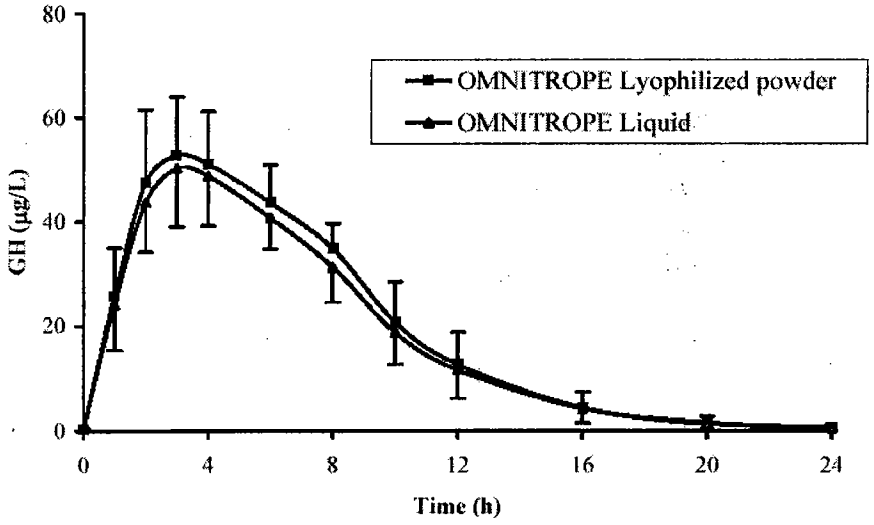
respectively). For an accurate assessment of the pharmacokinetics of Omnitrope^{AQ} and Omnitrope, endogenous growth hormone (GH) was suppressed by a continuous infusion of octreotide, starting one hour before administration of Omnitrope^{AQ} liquid formulation Omnitrope lyophilized powder formulation and lasted for a period of 25 hours.

The pharmacokinetic results showed that the confidence intervals for both Omnitrope PK parameters AUC and Cmax are lying entirely within the 80-125% bioequivalence range (Table 3 and Figure 3).

Table 3. Analysis of bioequivalence for PK parameters

Parameter	Omnitrope^{AQ} (Liquid) (N=24)	Omnitrope (lyophilized powder) (N=24)	Omnitrope^{AQ} / Omnitrope	90% CI
Cmax [µg/L]	51.7 ± 9.90	54.6 ± 12.9	94.7	90 - 99
AUCinf [µg/L•h]	426 ± 44.9	456 ± 44.1	93.4	90 - 97
Tmax (h)	3.9 ± 1.8	3.5 ± 1.3	-	-

Figure 3. hGH serum concentrations after sc injection of OMNITROPE™ Lyophilized powder and OMNITROPE™ Liquid (mean ± SD, n =12)



The pharmacodynamic responses, IGF-1 and IGFBP-3 following Omnitrope^{AQ} and Omnitrope showed confidence intervals for AUC and Cmax lying entirely within the bioequivalence range of 80-125%. Maximum PD observation occurred much later compared to the somatropin concentrations (Table 4, 5 and Figure 4, 5). The PK-PD relation was not further investigated.

Table 4. The pharmacodynamic response of somatropin: IGF-1. Results are presented as mean ± SD

Parameter	Omnitrope^{AQ} (Liquid) (N=24)	Omnitrope (lyophilized powder) (N=24)	Omnitrope^{AQ} / Omnitrope	90% CI
Cmax [µg/L]	264 ± 58	260 ± 53	102	97 - 106
AUC_{last} [h• µg /L]	19087 ± 4684	18806 ± 4381	101	97 - 106
Tmax (h)	22 ± 4	22 ± 7	-	-

Figure 4. IGF-1 serum concentrations after sc injection of OMNITROPE™ Lyophilized powder and OMNITROPE™ Liquid (mean ± SD, n = 24)

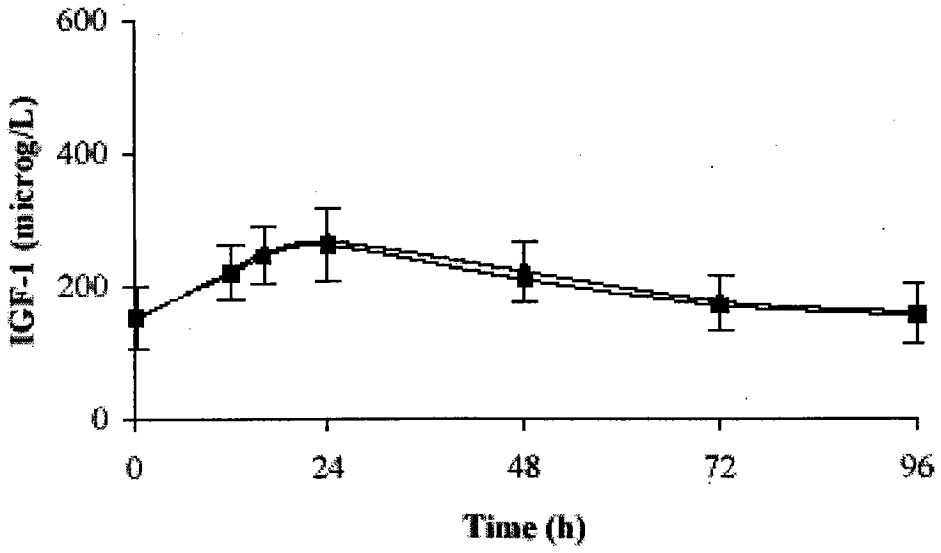
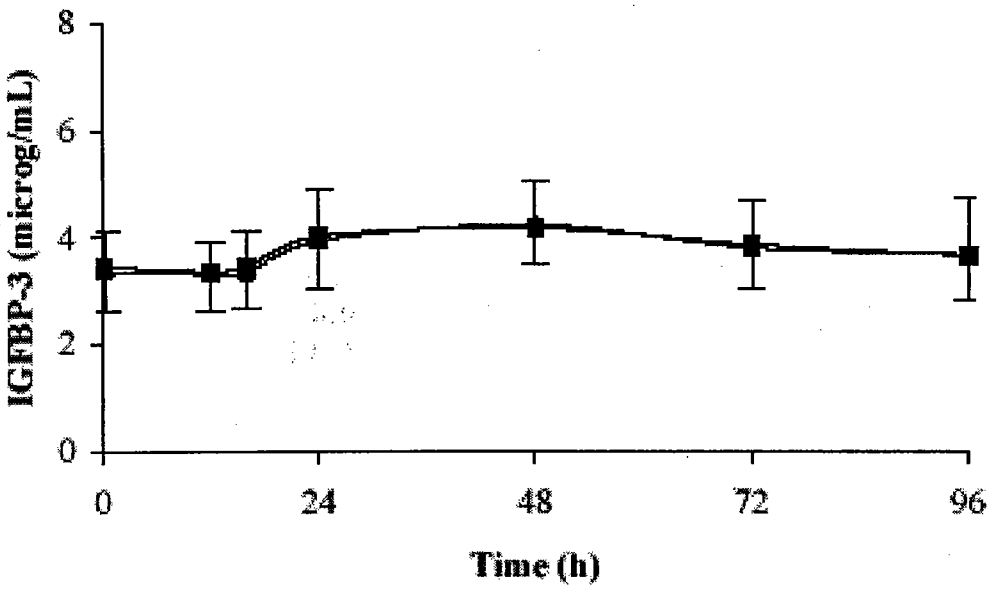


Table 5. The pharmacodynamic response of somatropin: IGFBP-3. Results are presented as mean ± SD

Parameter	Omnitrope^{AQ} (Liquid) (N=24)	Omnitrope (lyophilized powder) (N=24)	Omnitrope^{AQ} / Omnitrope	90% CI
Cmax [mg/L]	4 ± 1	4 ± 1	94.7	92 - 102
AUC_{last} [h•mg/L]	358 ± 69	362 ± 71	93.3	96 - 102
Tmax (h)	22 ± 4	22 ± 7	-	-

Figure 5. IGFBP-3 serum concentrations after sc injection of OMNITROPE™ Lyophilized powder and OMNITROPE™ Liquid (mean ± SD, n = 24)



Therefore, the study has determined that the two formulations are bioequivalent based on pharmacokinetic parameters. Although these two formulations are also equivalent based on pharmacodynamic responses measured by IGF-1 and IGFBP-3 using bioequivalence criteria, the reviewer is not convinced with this study design whether these PD parameters truly represent equivalence in terms of pharmacodynamics with the following reasons: (1) we don't know if the healthy human subject with octreotide treatment responds to Omnitrope in the same way as patients with GHD; (2) the dose of 5 mg Omnitrope used in the study was about 4 times the daily dose for adult GHD patients (0.0057 mg/kg/day vs. 5 mg/70kg=0.071 mg/kg). We don't know how the IGF-1 and other pharmacodynamic parameters respond to this supra pharmacologic dose. In order to claim pharmacodynamically equivalence, the sponsor should conduct a comparative study (additional arm or historic data) of PD parameters to the same dose used in adult GHD patients to validate their assumption.

2.5.2 Is Omnitrope lyophilized powder 5.8 mg formulation bioequivalent to Genotropin lyophilized powder 5.8 mg formulation?

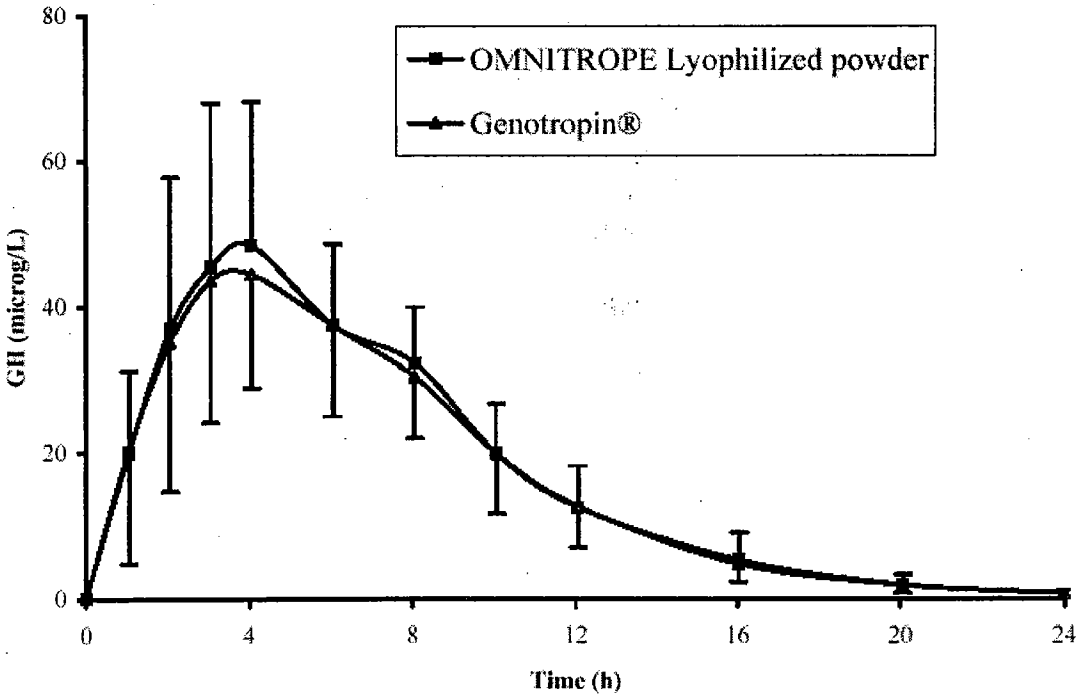
The sponsor conducted a double-blind, randomized, two-way cross-over, comparative study to compare the pharmacokinetics, pharmacodynamics of Omnitrope (test drug product) with that of Genotropin® (reference drug product) in 24 healthy male and female subjects after a single subcutaneous bolus injection of either 5.8 mg of Omnitrope or 5.8 mg of Genotropin®. To accurately assess the pharmacokinetics of Genotropin® and Omnitrope, endogenous growth hormone (GH) was suppressed by a continuous infusion of octreotide as previously described.

Both pharmacokinetic and pharmacodynamic parameters were maintained within 90% confidence intervals (Table 6 and Figure 6).

Table 6. Bioequivalence analysis of PK parameters for OMNITROPE™ Lyophilized powder and Genotropin®

Parameter	Test Product	Reference Product	90%
	Omnitrope	Genotropin	Confidence interval
Cmax	52 ± 21	48 ± 20	98 - 117
AUC_{inf} (h.ug/L)	416 ± 110	400 ± 105	100 - 108
Tmax	4.1 ± 1.6	4.9 ± 1.8	
T1/2	2.7 ± 0.6	2.9 ± 0.6	
CL/F (L/h)	13 ± 3	13 ± 4	

Figure 6. Growth hormone serum concentrations after subcutaneous injection of OMNITROPE™ Lyophilized powder (EP2000) and Genotropin™ (mean ± SD, n = 24)



The study has also demonstrated that the pharmacodynamic profiles of Omnitrope™ lyophilized powder and Genotropin™ are similar (Table 7).

Table 7. Pharmacodynamic parameters of growth hormone response (mean ± SD)

	Parameter	Omnitrope™ Lyophilised powder	Genotropin™	90% CI
IGF-1	Cmax (ug/L)	458 ± 159	428 ± 152	95-120
	AUC_{last} (h.ug/L)	31974 ± 10766	29893 ± 9569	99-114
	Tmax (h)	34 ± 24	32 ± 22	
IGFBP-3	Cmax (mg/L)	6 ± 2	5 ± 2	96-112
	AUC_{last} (h.mg/L)	420 ± 124	431 ± 148	92-106
	Tmax (h)	37 ± 26	47 ± 27	
NEFA	Cmax (mg/L)	36 ± 8	35 ± 10	92-114
	AUC_{last} (h.mg/L)	385 ± 154	395 ± 148	86-110
	Tmax (h)	4 ± 1	6 ± 3	

This study demonstrated that the 5.8 mg lyophilized formulation of Omnitrope™ (EP2000) developed by Biochemie GmbH is pharmacokinetically (Cmax, AUC_{inf}) bioequivalent to the 5.8 mg lyophilized formulation of Genotropin™ marketed by Pharmacia & Upjohn.

2.5.3 What is the relationship between clinical trials and formulations? Do we accept the modified to-be-marketed formulation?

Omnitrope was initially produced by [redacted] In the later phase of clinical trials, the production of drug substance, Omnitrope was made in Biochemie, Austria. Three lyophilized powder formulations used in the phase 3 pivotal clinical trials were identical (Table 8).

Table 8. Composition of clinical formulations

Composition	OMNITROPE 5.8 mg Lyophilized powder Batch [S00200]		OMNITROPE 5.8 mg Lyophilized powder Batch [594403A]		OMNITROPE 5.8 mg Lyophilized powder Batch [551533A]	
	EP2K-99-PhIII		EP2K-00-PhIIIFo		EP2K-00-PhIII^{AQ}	
	Amount per vial	Amount in 1 mL of reconstituted solution	Amount per vial	Amount in 1 mL of reconstituted solution	Amount per vial	Amount in 1 mL of reconstituted solution
Active ingredient Recombinant Somatropin	5.8 mg	5.0 mg (15 IU)	5.8 mg	5.0 mg (15 IU)	5.8 mg	5.0 mg (15 IU)
Other ingredients Glycine	27.6 mg	23.8 mg	27.6 mg	23.8 mg	27.6 mg	23.8 mg
Sodium dihydrogen phophate dehydrate	0.96 mg	0.83 mg	0.96 mg	0.83 mg	0.96 mg	0.83 mg
Disodium phosphate Heptahydrate	1.4 mg	1.2 mg	1.4 mg	1.2 mg	1.4 mg	1.2 mg
Sodium hydroxide	q.s.	q.s.	q.s	q.s.	q.s.	q.s.
Water for injection	-[1]	965.17 mg	-[1]	965.17 mg	-[1]	965.17 mg
Benzyl alcohol	-	15 mg	-	15 mg	-	15 mg
[redacted]	q.s.	-	q.s.	-		q.s.

[redacted]

The sponsor has made some changes in the composition of two phosphates in the to-be-marketed formulation (Table 9). However, the two phosphates can not be differentiated, and in both compositions the resulting phosphate concentration is constant at 10 mM (9.98 mM for the composition used for the phase 3 clinical trials, and 9.99 mM for the composition intended for to-be-marketed). The final pH remains the same as 7.0. The reviewer agrees that this modification will not alter the rate and extent of absorption.

Table 9. Composition of clinical and to-be-marketed formulations of 5.8 mg Omnitrope

Ingredient	Composition of batch [594403A] Amount per vial	Composition to be marketed Amount per vial
Active ingredient Recombinant somatropin	5.8 mg (17.4 I.U.) [2, 3]	5.8 mg (17.4 I.U.) [2, 3]
Other ingredients Sodium dihydrogen phosphate[1] dihydrate	0.96 mg [4] (6.15 µmol)	0.56 mg [4] (3.59 µmol)
Disodium hydrogen phosphate heptahydrate	1.4 mg [4] (5.22 µmol)	2.09 mg [4] (7.80 µmol)
Glycine	27.6 mg	27.6 mg
Sodium hydroxide Water for injection	q.s. [5]	q.s. [5]
Benzyl alcohol	15 mg	15 mg
	q.s.	q.s.

[1]Recombinant somatropin is supplied as BC rhGH bulk solution containing 10 mg rhGH/mL, 1.697 mg Na2HPO4 x 7H2O/mL, and 0.569 mg NaH2PO4 x 2H2O/mL and water for injections [redacted]

[2]Ph. Eur.: 1 mg of anhydrous somatropin (C990H1528N262O300S7) is equivalent to 3.0 I.U. of biological activity.

[3] After reconstitution with 1.14 mL of the solvent (Solvent for parenteral use "Cartridge Benzyl Alcohol") the concentration of the active substance in the reconstituted solution is 5.0 mg/mL (15 IU/mL).

[4] Including the phosphate from the BC rGH bulk solution.

[redacted]

Table 10 summarizes the relationship between the phase 3 clinical trials, drug substance and formulations.

Table 10. Clinical Trials and formulations

	Pivotal studies for NDA submission				Supportive data	To-be-marketed
Month	**0 - 6**	**6 - 9**	**9 - 15**		**15 - 24**	
Clinical trial	EP2K-99-PhIII	EP2K-00-PhIIIFo	EP2K-00-PhIII^{AQ} (Part A)		EP2K-00-PhIII^{AQ}(Part B)	
Formulation	Lyophilized powder	Lyophilized powder	Liquid	Lyophilized powder	Liquid	Lyophilized powder
Drug substance	Covance/ [redacted]		Biochemie, Kundl, Austria			Biochemie, Austria, and formulation by Novartis in Stein, Switzerland
BE		**Bioequivalent**				

2.5.4 Can a BE study for Omnitrope™ 1.5 mg lyophilized powder be waived?

Omnitrope 1.5 mg lyophilized powder has not been used in any clinical trials by the sponsor. The sponsor has proposed that Omnitrope 1.5 is more appropriate for very young children than Omnitrope 5.8, as the diluents for Omnitrope 5.8 contains benzyl alcohol. Since the treatment of neonates and infants with preparations containing benzyl alcohol is contraindicated, these patients can, in the alternative, be treated with Omnitrope 1.5 mg lyophilized powder which does not contain any benzyl alcohol and is intended for single use only. However, the rule to grant a BE waiver is based on the exact proportionality of composition between high and low strength formulations to waive a bioequivalence study between these two strengths. The comparison of Omnitrope lyophilized powder 5.8 mg and 1.5 mg formulations is presented in the Table 11.

Table 11. Composition of Omnitrope lyophilized powder 5.8 mg and 1.5 mg formulations

Ingredient	Function	Amount per vial	
		Omnitrope 5.8 mg	**Omnitrope 1.5 mg**
Recombinant hGH	Active substance	5.8 mg (17.4 IU)	1.5 mg (4.5 IU)
Other ingredients			
[redacted]			

[redacted]	[redacted]		
[redacted]	[redacted]	q.s.	q.s.
Benzyl alcohol	preservative	15 mg	-
Water for Injection	Solvent	[2]	[2]

[1] Including the phosphate from the BC r-hGH bulk solution.

[redacted]

Because the composition of these two formulations is not proportional, the rate and extent of absorption of these two formulations can not be assured to be bioequivalent. Therefore, a BE waiver can not be granted. As a consequence, it's recommended that Omnitrope™ lyophilized powder 1.5 mg not be approved for marketing.

2.6 ANALYTICAL

2.6.1 Analysis of Omnitrope

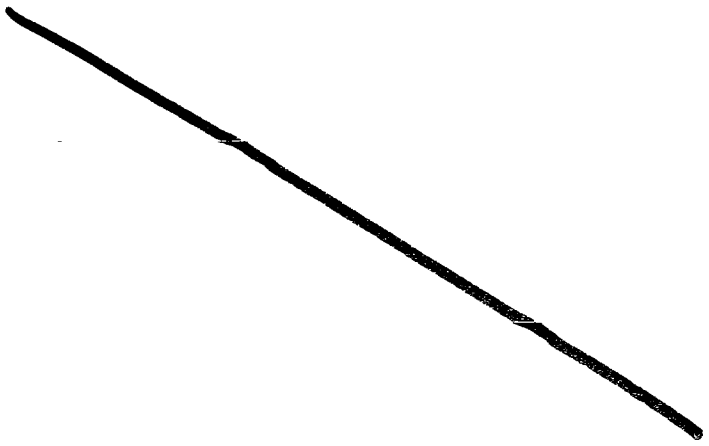
[redacted]

Table 12. Assay validation results for serum Omnitrope samples

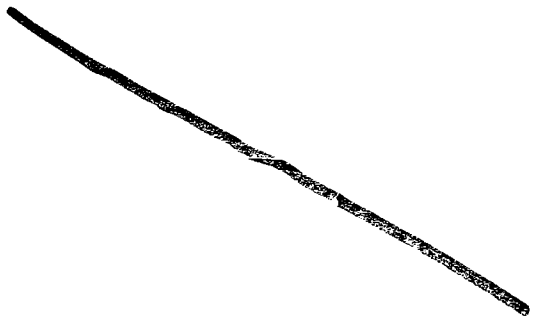
Precision (%CV)	4.2 – 8.4%
Accuracy	100.2 – 111.3%
Linearity	0.2 – 20.0 ng/mL
Sensitivity	LOQ: 0.2 ng/mL
Specificity	No crossreactivities from serum LH, FSH, Prolactin, TSH, HCG (<0.01%), HPL (<0.14%)
Stability (1) Freeze/thaw x 7	93.5 - 109% activity retained

(2) Refrigerated temperature (2° – 8°C)	93.5 – 104.3% activity retained
(3) Room temperature(20° – 25°C)	95.4 – 103.2% activity retained
(4) Frozen temperature (-15° – -35°C)	102.6% activity retained
(5) Hemolysis	93.5 – 105.5% activity retained

2.6.2 Analysis of serum IGF-1



2.6.3 Analysis of serum IGFBP-3



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✓ Trade Secret / Confidential

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3 DETAILED LABELING RECOMMENDATIONS

N/A

4 APPENDICES

4.1 PROPOSED LABELING

Not attached

4.2 INDIVIDUAL STUDY REVIEW

EP2K-99-PhISUSA study

Title of Study: A Phase I Safety Study in Healthy Volunteers to Assess the Safety, Tolerance and Pharmacokinetics of EP2000 after Single Subcutaneous Administration

Principal Investigator: Philip T Leese, MD

Study Center: Quintiles Phase I unit, 11250 Corporate Avenue, Lenexa, Kansas, USA

Study dates: October 22, 1999 to November 6, 1999 **Phase of development:** Phase I

Objectives: The study objectives were: (1) to assess the safety and tolerance of EP2000 after single dose administration, (2) to assess the pharmacokinetics and pharmacodynamics of EP2000; (3) to validate the pharmacokinetic and pharmacodynamic model to be used in a subsequent Phase I comparative study of EP2000 with Genotropin in order to demonstrate the pharmaceutical equivalence of the two preparations after subcutaneous administration.

Methodology: This was a double-blind, randomized, placebo-controlled, two-way cross-over study to assess the safety, tolerance and pharmacokinetics of EP2000. There were ten study visits, screening (Visit 1), four visits in each of the two treatment periods (Visit 2 to 5, and Visit 6 to 9) separated by a washout period of 1 week, and a follow-up visit (Visit 10). To accurately assess the pharmacokinetics of EP2000, endogenous growth hormone (GH) was suppressed by a continuous infusion of octreotide. At the treatment visits, subjects received a subcutaneous (SC) bolus injection of either EP2000 or placebo.

Diagnosis and main criteria for inclusion: Healthy male and female subjects, aged 18-45 years, with no clinically relevant laboratory abnormalities and with normal electrocardiogram (ECG), or ECG without clinically significant findings, blood pressure (BP) and pulse rate (PR) at the screening visit (Visit 1) were enrolled into the study. Subjects had to provide written informed consent and have a negative drugs-of-abuse screen.

Test product, dose and mode of administration, batch numbers:
EP2000 (recombinant human GH), 5 mg, SC bolus injection, batch number 551553A.

Reference therapy, dose and mode of administration, batch number:
Placebo (water for injection), 1 ml, SC bolus injection, Fujisawa lot number 370524 (exp. 11/00).

Pharmacokinetic/Pharmacodynamic Assessments:
(1) Assessment of the pharmacokinetic parameters of EP2000, Cmax, tmax, AUClast (or AUC0-24) and t½, as measured by EP2000 serum concentrations up to 24 hours post-

dose. (2) Assessment of the pharmacodynamic response to EP2000 as determined by IGF-1 and IGFBP-3 serum concentrations up to 96 hours post-dose and NEFA serum concentrations up to 24 hours post-dose.

Pharmacokinetic Results

A constant iv infusion of octreotide is effective to suppress completely the endogenous secretion of GH in healthy volunteers ((Figure 1, Table 1). No statistical differences for pharmacokinetic parameters between males and females (Table 2).

Figure 1. The EP2K-99-PhISUSA study demonstrated that continuous iv infusion of octreotide is effective in completely suppressing endogenous hGH secretion in healthy human volunteers.

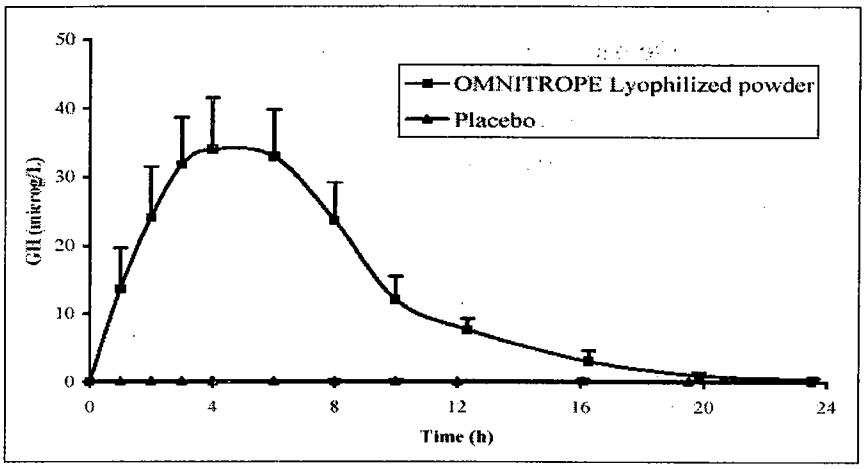


Table 1: EP2K-99-PhISUSA study: compartmental analysis of hGH pharmacokinetics after single sc injection of Omnitrope™ Lyophilized powder 5 mg.

	t_{lag} (h)	C_{max} (µg/L)	t_{max} (h)	AUC_{inf} (h·µg/L)	k_a (h^{-1})	$t_{1/2}$ (h)	CL/F (L/h)
Mean	0.7	37	3.6	291	0.4	2.4	18
SD	0.5	9	0.5	42	0.2	0.4	3
Median	0.5	37	3.5	290	0.4	2.4	17
Min	0.4	21	2.9	206	0.3	1.6	14
Max	2.2	55	4.5	350	0.7	3.3	24

Table 2: EP2K-99-PhISUSA study: effect of gender on the pharmacokinetic parameters of Omnitrope™ Lyophilized powder (n = 12, female = 6, male = 6)

	Gender	t_{lag} (h)	C_{max} (µg/L)	t_{max} (h)	AUC_{inf} (h·µg/L)	k_a (h^{-1})	$t_{1/2}$ (h)	CL/F (L/h)
Mean	Female	0.8	40	3.7	311	0.5	2.3	16
	Male	0.6	33	3.5	270	0.4	2.5	19
Median	Female	0.5	39	3.7	316	0.4	2.2	16
	Male	0.5	36	3.4	273	0.3	2.5	18
Kruskal-Wallis (p value)		0.7	0.2	0.8	0.1	0.7	0.5	0.1

Pharmacodynamic Results:

The pharmacodynamic responses (IGF-1, IGFBP-3, NEFA) after administration of EP2000 5 mg and of placebo are statistically different for C_{max} and AUC_{last}. After the sc injection of EP2000, IGF-1 and IGFBP-3 return to baseline after 96 hours and NEFA returns to baseline after 24 hours, There is a correlation between GH C_{max} and IGF-1 C_{max} (r = -0.6) and GH AUC_{last} and IGF-1 AUC_{last} (r = -0.6), There is no correlation between GH C_{max} and IGFBP-3 and NEFA C_{max} (r = -0.1 and 0.2, respectively), and GH AUC_{last} and IGFBP-3 and NEFA AUC_{last} (r = -0.3 and -0.1, respectively).

Table 3: Pharmacodynamic response (IGF-1, IGFBP-3 and NEFA) after single sc injection of Omnitrope™ Lyophilized powder 5 mg and placebo

		IGF-1			IGFBP-3			NEFA		
		C_{max} (µg/L)	t_{max} (h)	AUC_{last} (µg/L·h)	C_{max} (mg/L)	t_{max} (h)	AUC_{last} (mg/L·h)	C_{max} (mg/dL)	t_{max} (h)	AUC_{last} (mg/dL·h)
OMNITROPE™ Lyophilized powder	Mean	424	34	31890	5.0	43	399	39	5	409
	SD	163	15	11415	1.0	15	71	9	3	130
	Median	367	36	26912	5.0	48	386	37	4	386
	Min	256	16	20935	3.7	16	292	27	2	288
	Max	818	48	52946	6.6	71	498	58	12	789
Placebo	Mean	279	44	21674	4.2	39	344	18	2	114
	SD	107	40	8491	0.9	33	68	6	1	51
	Median	253	32	18506	3.9	24	316	15	2	106
	Min	144	0	11742	2.6	0	239	9	1	51
	Max	546	97	40945	5.5	96	457	33	4	218
Wilcoxon test (p value)		0.002	0.2	0.002	0.006	0.6	0.003	0.002	0.003	0.002

Figure 2: Correlation between GH C_{max} and IGF-1 C_{max}, and between GH AUC_{last} and IGF-1 AUC_{last} (_ female, _ male)

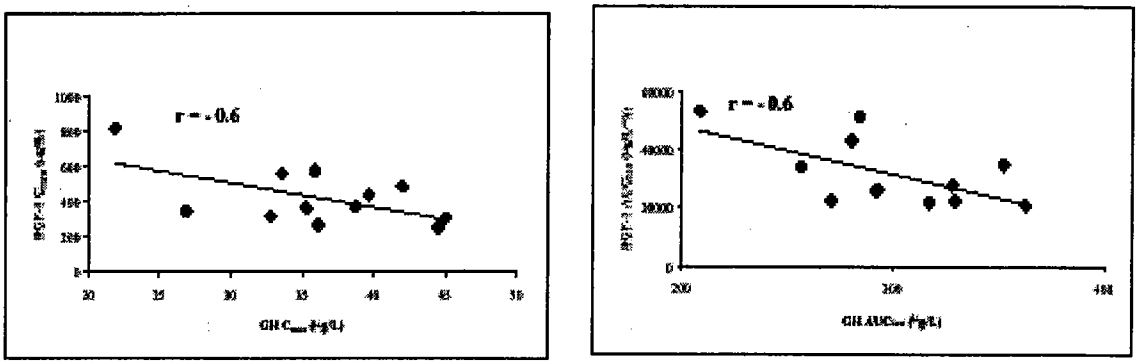


Figure 3: Correlation between GH C_{max} and IGFBP-3 C_{max}, and between GH AUC_{last} and IGFBP-3 AUC_{last} (_ female, _ male)

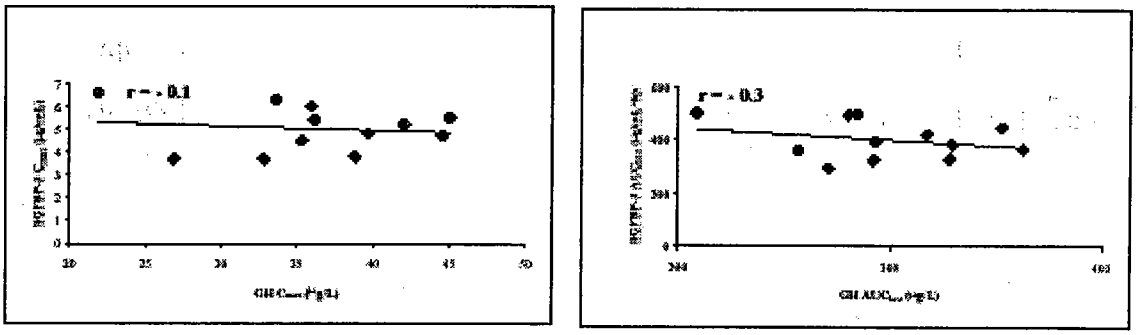
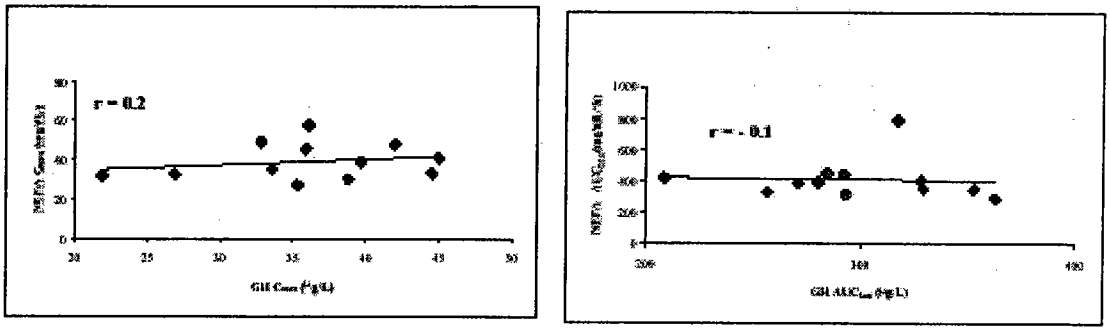


Figure 4: Correlation between GH C_{max} and NEFA C_{max}, and between GH AUC_{last} and NEFA AUC_{last} (_ female, _ male)



Conclusion:

This study demonstrated that continuous iv infusion of octreotide is effective to suppress completely endogenous secretion of GH. The pharmacokinetics of EP2000 is well described by a one-compartment model t_{lag} = 0.7 ± 0. 5 h (mean ± SD), C_{max} = 37 ± 9 µg/L, t_{max} = 3.6 ± 0.5 h, AUC_{inf} = 291 ± 42 h* µg /L, k_a = 0.4 ± 0.2 h^{-1}, $t_{1/2}$ = 2.4 ± 0.4 h, and CL/F = 18 ± 3 L/h. Gender has no effect on the pharmacokinetic parameters of EP2000. The study also validated the chosen pharmacodynamic markers demonstrating that a single sc administration of 5 mg of BC r-hGH induces significant increases in IGF-1, IGF-BP3 and NEFA which return to baseline within 96 h, 96 h and 24 h, respectively.

Reviewer's comments:

This study has demonstrated that the secretion of human growth hormone is suppressed completely by continuous intravenous administration of octreotide at a rate of 0.04 mg/hour, which simulates a condition of growth hormone deficiency. Therefore, a bioequivalence study conducted in such a setting would be similar to a BE study conducted in patients with growth hormone deficiency from the point view of pharmacokinetics.

Individual Study Reviews

EP2K-00-PhI[AQ]

Title: A phase I, double-blind, randomized, 2-way cross-over pharmacokinetic study to assess the bioequivalence of EP2000 (lyophilized powder formulation) and EP2000 AQ (liquid formulation) in 24 healthy volunteers after single subcutaneous administration and compare the pharmacodynamics and the safety of the two treatments.

Investigational products: Liquid formulation of EP2000 AQ (test formulation); lyophilized powder formulation of EP2000 (reference formulation)

Objectives:
Primary objective was to establish the bioequivalence of the liquid formulation of EP2000 AQ , a new preparation of r-hGH (test formulation) and the lyophilized powder formulation of EP2000 (reference formulation), as assessed by a specific chemiluminescence assay.

Methodology:
This was a double-blind, randomized, two-way cross-over study to establish the bioequivalence of EP2000 AQ liquid formulation and EP2000 lyophilized powder formulation and to compare the pharmacodynamics and safety of the two preparations. There were two treatment periods, separated by a wash-out period of at least one week. In total, each subject visited the study centre on 10 separate occasions: screening, four visits in each of the two treatment periods and at follow-up. At the treatment periods (Visit 2 to 5, and Visit 6 to 9), subjects received a SC bolus injection of either EP2000 AQ liquid formulation or EP2000 lyophilized powder formulation. For an accurate assessment of the pharmacokinetics of EP2000 AQ and EP2000, endogenous growth hormone (GH) was suppressed by a continuous infusion of octreotide, starting one hour before administration of EP2000 AQ liquid formulation or EP2000 lyophilized powder formulation and lasted for a period of 25 hours.

Test product, dose and mode of administration, batch numbers: EP 2000 AQ liquid formulation (recombinant human GH), 5 mg, administered as SC bolus injection.

Criteria for Evaluation:
Pharmacokinetic/Pharmacodynamic Assessments:
(1) Bioequivalence of EP2000 AQ (liquid formulation) and EP2000 (lyophilized powder formulation) was assessed by the pharmacokinetic parameters AUC0-∞ (or AUC0-24), Cmax and tmax measured from GH serum concentrations up to 24 hours post-dose.

(2) Pharmacodynamic response to EP2000 AQ and EP2000 as assessed by Cmax, AUC0-last and tmax of the serum concentrations of IGF-1 and IGFBP-3 (up to 96 hours post-

dose) and NEFA (up to 24 hours post-dose). Differences from baseline were calculated for Cmax and AUC0-last (Cmax and .AUC0-last, respectively)

Pharmacokinetic Results:
The low variability of somatropin PK parameters AUC and Cmax of about 10% lead to confidence intervals lying entirely within the 80-125% bioequivalence acceptance range, but not including the 100% ratio. This means that the 7% difference of extent of somatropin exposure following EP2000 AQ compared to the administration of EP2000 is statistically significant.

The confidence interval for tmax is entirely within the 80 to 120% range including the 100% value and thus demonstrates equivalent tmax values. This is a remarkable result for this parameter showing a high overall variability. The small confidence interval is caused by the subjects showing a high inter-individual variability and a low intra-individual variability. Somatropin half-life remained unchanged.

Figure 1: Mean Somatropin Plasma Concentrations

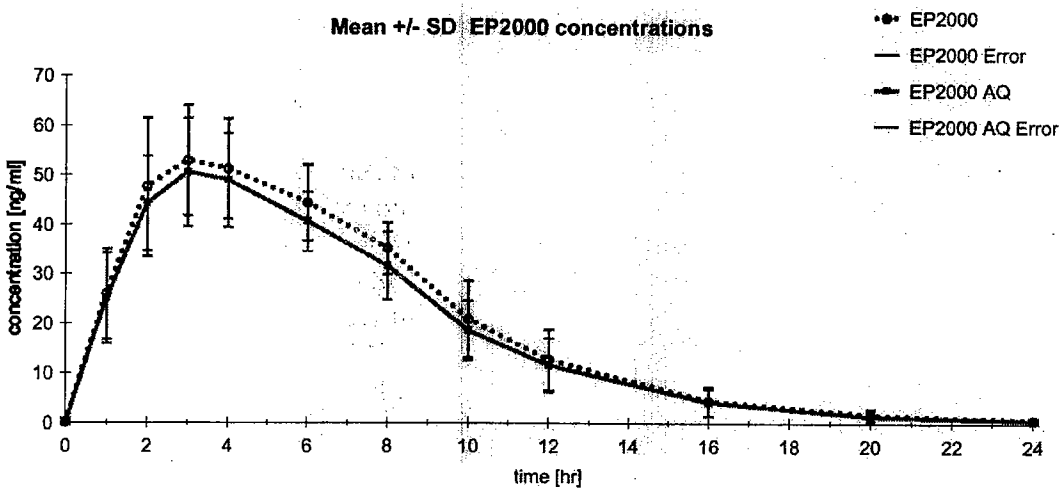


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Table 4: Summary of Somatropin Pharmacokinetic Parameters

Summary of Somatropin Pharmacokinetic Parameters				
	EP2000 ^{AQ} (N=24)		EP2000 (N=24)	
Parameter	geo.Mean	SD	geo.Mean	SD
AUC(0-24) [ng*h/ml]	422	44.7	453	43.4
AUC(0-∞) [ng*h/ml]	426	44.9	456	44.1
C_{24h} [ng/ml]	0.436	0.372	0.512	0.304
Cmax [ng/ml]	51.7	9.90	54.6	12.9
	EP2000 ^{AQ} (N=24)		EP2000 (N=24)	
Parameter	Mean	SD	Mean	SD
λz [1/h]	0.314	0.072	0.307	0.078
t1/2 [h]	2.35	0.668	2.40	0.644
tmax [h]	3.54	1.28	3.92	1.79

values taken from Table 17 (Section 14)

Table 5: Statistical Results of Somatropin Bioequivalence Testing

	Point	LS-Mean	LS-Mean	90%Confidence Interval	
Parameter	Estimator	EP2000^{AQ}	EP2000	Lower	Upper
AUC [ng*h/ml]	93.3	426	456	90.1	96.6
AUC(0-24) [ng*h/ml]	93.1	422	453	89.9	96.5
Cmax [ng/ml]	94.8	51.7	54.6	90.3	99.4
tmax$^{(1)}$ [h]	100	3.00	3.00	81.7	115
values taken from Table 21 (Section 14)					

(1) distribution free statistical procedure

Pharmacodynamic Results:

The IGF-1, IGFBP-3 and NEFA concentrations following EP2000 AQ and EP2000 show confidence intervals for AUC and Cmax lying entirely within the bioequivalence acceptance range of 80-125% and including 100%. Thus, the IGF-1, IGFBP-3 and NEFA plasma concentration profiles demonstrate EP2000 AQ and EP2000 producing equivalent pharmacodynamic response. There was no direct link of pharmacodynamic parameters IGF-1, IGFBP-3 and NEFA to the Somatropin results. Maximum PD observation occurred much later compared to the somatropin concentrations. The PK-PD relation was not further investigated, since for the primary objective of this study it is only important to get equal PD responses following the two formulations tested.

Table: Pharmacodynamic parameters of Somatropin. Results are presented as mean ± SD.

		EP2K-00-PhIAQ	
		OMNITROPE™ Lyophilized powder	**OMNITROPE™ Liquid**
IGF-1	C_{max} (µg/L)	*260 ± 53	*264 ± 58
	t_{max} (h)	22 ± 7	22 ± 4
	AUC_{last} (h·µg/L)	*18806 ± 4381	*19087 ± 4684
	90% confidence intervals	log C_{max}: 97 → 106 log AUC_{last}: 97 → 106	
IGFBP-3	C_{max} (mg/L)	*4 ± 1	*4 ± 1
	t_{max} (h)	22 ± 7	22 ± 4
	AUC_{last} (h·mg/L)	*362 ± 71	*358 ± 69
	90% confidence intervals	log C_{max}: 92 → 102 log AUC_{last}: 96 → 102	
NEFA	C_{max} (mEq/L)	0.85 ± 0.3	0.93 ± 0.3
	t_{max} (h)	4 ± 2	4 ± 1
	AUC_{last} (h·mEq/L)	11 ± 4	11 ± 4
	90% confidence intervals	log C_{max}: 97 → 122 log AUC_{last}: 88 → 112	

* Geometric mean

There was no direct link of pharmacodynamic parameters IGF-1, IGFBP-3 and NEFA to the somatropin results. Maximum PD observation occurred much later compared to the somatropin concentrations. The PK-PD relation was not further investigated, since for the primary objective of this study it is only important to get equal PD responses following the two formulations tested.

Conclusion:

The study demonstrated that OMNITROPETM Liquid is bioequivalent to the 5 mg lyophilized formulation of OMNITROPETM in terms of pharmacokinetics (hGH Cmax, AUCinf and tmax) and pharmacodynamics (IGF-1, IGFBP-3, NEFA Cmax, AUClast and tmax).

EP2K-99-PhIUSA study

Title: A phase I, double-blind, randomized, 2-way crossover study of EP2000 and Genotropin® in 24 healthy volunteers after single subcutaneous administration to compare the pharmacokinetics, pharmacodynamics and safety of the two treatments.

Principal Investigator: Philip T Leese, MD

GCP Statement: This study was conducted in accordance with Good Clinical Practices (GCP) for Trials of Medicinal Products and with International Conference of Harmonization (ICH) Guidelines for GCP (CPMP/ICH/135/95), including archiving of essential study documents.

Date of the report: July 20, 2000

Objectives: (1) To compare the pharmacokinetics of EP2000, a new preparation of r-hGH (test formulation), to that of Genotropin® (reference formulation), as assessed by a specific immunoassay. (2) To compare the pharmacodynamics of EP2000 with Genotropin® in terms of IGF-1 serum profile, IGFBP-3 serum profile, and NEFA serum profile. (3) To compare the safety of the test formulation (EP2000) to that of the reference formulation (Genotropin®).

Methodology: This was a double-blind, randomized, two-way cross-over, comparative study to compare the pharmacokinetics, pharmacodynamics and safety of EP2000 with that of Genotropin®. There were ten study visits, screening (Visit 1), four visits in each of the two treatment periods (Visit 2 to 5, and Visit 6 to 9) separated by a washout period of 1 week, and a follow-up visit (Visit 10). To accurately assess the pharmacokinetics of Genotropin® and EP2000, endogenous growth hormone (GH) was suppressed by a continuous infusion of octreotide. At the treatment visits, subjects received a subcutaneous (SC) bolus injection of either EP2000 or Genotropin®.

Number of subjects: 25 (12 males, 13 females). One female withdrew during treatment period 1 and was replaced.

Test product, dose and mode of administration, batch numbers:
EP2000 (recombinant human GH), 5 mg, SC bolus injection.

Reference therapy, dose and mode of administration:
Genotropin®, 5 mg, SC bolus injection.

Pharmacokinetic/Pharmacodynamic Assessments:
(1) Assessment of the pharmacokinetic parameters Cmax, tmax and AUC0-_ (or AUC0-24), as measured by EP2000 and Genotropin® serum concentrations up to 24 hours post-dose. (2) Assessment of the pharmacodynamic response to EP2000 and Genotropin® as determined by Cmax, tmax, AUC0-last of IGF-1 and IGFBP-3 serum concentrations up to 96 hours post-dose and NEFA serum concentrations up to 24 hours post-dose, and by

the difference from baseline for Cmax and AUC0-last (Cmax and AUC0-last, respectively).

Pharmacokinetic results:

This study demonstrated comparable pharmacokinetic parameters between Omnitrope and Genotropin with a Cmax of approximately 50µg/L reached in 4 hours, a half life of 2.7 h and a CL/F of 13 L/h. The pharmacokinetic bioequivalence was observed between EP2000 and Genotropin in term of Cmax and AUCinf and there was no significant difference between EP2000 and Genotropin for tmax and no statistical differences for Cmax and tmax between males and females but statistical differences for AUC, Vz, CL/F,

Figure 1: GH serum concentrations after subcutaneous injection of EP2000 and Genotropin (mean _ SD, n = 24)

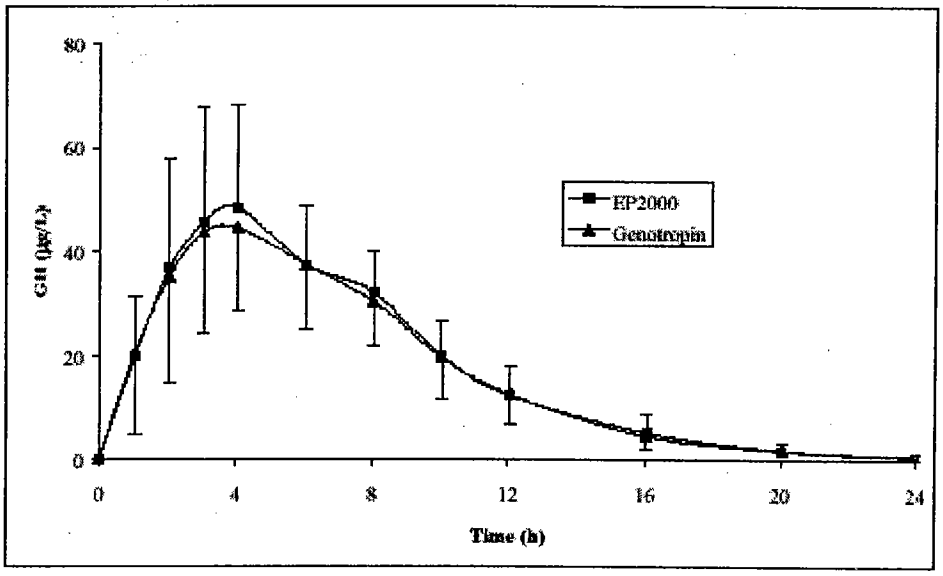

Table 1: Non-compartmental analysis of GH pharmacokinetics after sc injection of EP2000 and Genotropin_ (n = 24)

		C_{max} (µg/L)	t_{max} (h)	AUC_{last} (h*µg/L)	AUC_{inf} (h*µg/L)	$t_{1/2}$ (h)	Vz (L)	CL/F (L/h)	MRT_{last} (h)	MRT_{inf} (h)
EP2000	Mean	52	4.1	413	416	2.7	52	13	7.0	7.1
	SD	21	1.6	111	110	0.6	24	3	1.3	1.5
	Median	45	4.1	387	391	2.5	43	13	6.6	6.6
	Min	24	2.1	217	220	2.0	21	7	4.9	4.9
	Max	96	8.1	717	718	4.0	119	23	9.3	9.9
Genotropin*	Mean	48	4.9	396	400	2.9	57	13	7.0	7.2
	SD	20	1.8	106	105	0.6	27	4	1.2	1.3
	Median	44	4.1	391	393	2.7	50	13	7.0	7.1
	Min	21	2.0	208	211	2.1	24	7	3.9	4.0
	Max	108	10.1	696	697	4.6	142	24	9.2	10.2
Wilcoxon test	(p value)		0.052							

Table 2: Analysis of variance on log transformed Cmax and log transformed AUCinf of EP2000 and Genotropin and 90% Confidence intervals

	Effect	Probability	90% Confidence interval
Log C_{max}	Sequence	0.3	
	Volunteer (sequence)	0.0001	
	Period	0.6	
	Treatment (Genotropin® vs EP2000)	0.2	98 → 117
Log AUC_{inf}	Sequence	0.1	
	Volunteer (sequence)	0.0001	
	Period	0.9	
	Treatment (Genotropin® vs EP2000)	0.1	100 → 108

Table 5: Effect of gender on the pharmacokinetic parameters of EP2000 and Genotropin®

			C_{max} (µg/L)	t_{max} (h)	AUC_{last} (h*µg/L)	AUC_{inf} (h*µg/L)	$t_{1/2}$ (h)	Vz (L)	CL/F (L/h)	MRT_{last} (h)	MRT_{inf} (h)
EP2000	Mean	Female	61	4	463	465	3	42	11	7	7
		Male	43	4	362	366	3	62	14	7	7
	Median	Female	53	4	450	451	2	42	11	6	6
		Male	42	4.1	377	380	3	49	13	7	7
Kruskal-Wallis	(p value)		**0.08**	**0.5**	**0.04**	**0.04**	**0.2**	**0.05**	**0.05**	**0.3**	**0.3**
Genotropin®	Mean	Female	56	5	450	453	3	44	12	7	7
		Male	40	5	342	346	3	70	15	7	8
	Median	Female	49	4	415	419	2	44	12	7	7
		Male	40	5	360	362	3	56	14	8	8
Kruskal-Wallis	(p value)		**0.06**	**0.5**	**0.01**	**0.01**	**0.08**	**0.02**	**0.02**	**0.2**	**0.2**

Pharmacodynamic Results

The pharmacodynamic bioequivalence between EP2000 and Genotropin was established in term of IGF-1, IGFBP-3 and NEFA Cmax and AUCinf and no significant difference between IGF-1, IGFBP-3 and NEFA for tmax,

Figure 4: IGF-1 serum concentrations after subcutaneous injection of EP2000 and Genotropin_ (mean ± SD, n = 24)

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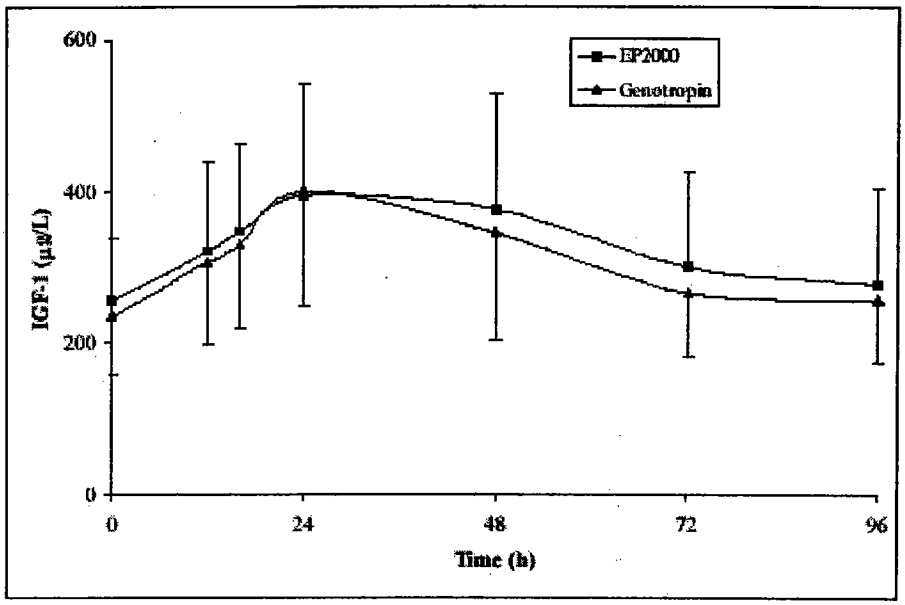

IGF-1 parameters are summarised in Table 6, ANOVA and 90% confidence intervals are presented in Table 7. Individual graphs, individual parameters, bioequivalence tests and Wilcoxon test are included in Appendices

Table 6: Pharmacodynamic response (IGF-1) after sc injection of 5 mg of EP2000 and Genotropin

		C_{max} IGF-1 (µg/L)	t_{max} IGF-1 (h)	AUC_{last} IGF-1 (µg/L*h)	ΔC_{max} IGF-1 (µg/L)	ΔAUC_{last} IGF-1 (µg/L*h)
EP2000	Mean	458	34	31974	204	7761
	SD	159	24	10766	127	6279
	Median	425	24	29970	181	6343
	Min	197	12	15521	47	340
	Max	759	97	51684	562	24138
Genotropin®	Mean	428	32	29893	193	7384
	SD	152	22	9569	127	5187
	Median	385	24	28894	161	6124
	Min	219	12	16288	42	1447
	Max	750	96	52810	477	17235
Wilcoxon test (p value)			0.6			

Table 7: Analysis of variance on IGF-1 log transformed Cmax and IGF-1 log transformed AUClast of EP2000 and Genotropin_ and 90% confidence intervals

	Effect	Probability	90% Confidence Interval
Log C_{max}	Sequence	0.01	
	Volunteer (sequence)	0.002	
	Period	0.4	
	Treatment (Genotropin® vs EP2000)	0.4	95→ 120
Log AUC_{last}	Sequence	0.001	
	Volunteer (sequence)	0.0001	
	Period	0.8	
	Treatment (Genotropin® vs EP2000)	0.2	99→ 114

Figure 5: IGFBP-3 serum concentrations after subcutaneous injection of EP2000 and Genotropin_ (mean _ SD, n = 24)

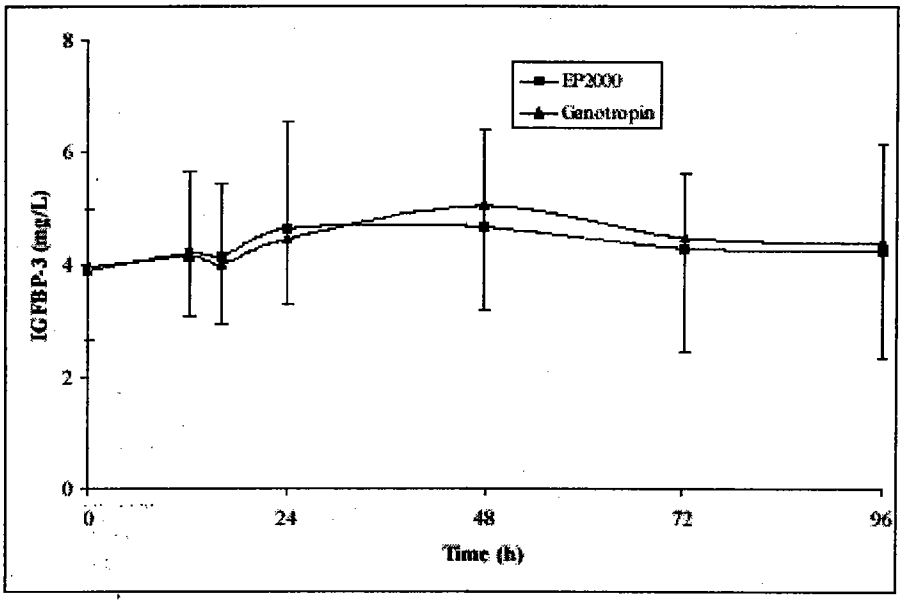

Table 8: Pharmacodynamic response (IGFBP-3) after sc injection of 5 mg of EP2000 and Genotropin

		C_{max} IGFBP-3 (mg/L)	t_{max} IGFBP-3 (h)	AUC_{last} IGFBP-3 (mg/L*h)	ΔC_{max} IGFBP-3 (mg/L)	ΔAUC_{last} IGFBP-3 (mg/L*h)
EP2000	Mean	5.6	37	420	1.7	58
	SD	2.1	26	124	1.5	62
	Median	5.4	24	432	1.1	34
	Min	2.6	0	201	0.0	0
	Max	11.1	97	660	6.4	249
Genotropin®	Mean	5.3	47	431	1.4	67
	SD	1.9	27	148	1.2	71
	Median	5.2	48	453	1.1	53
	Min	2.0	0	137	0.0	0
	Max	11.9	97	885	5.6	324
Wilcoxon test (p value)			0.3			

Table 9: Analysis of variance on IGFBP-3 log transformed C_{max} and IGFBP-3 log transformed AUC_{last} of EP2000 and Genotropin_ and 90% confidence intervals on the ratio of means

	Effect	Probability	90% Confidence Interval
Log C_{max}	Sequence	0.02	
	Volunteer (sequence)	0.0001	
	Period	0.9	
	Treatment (Genotropin® vs EP2000)	0.4	96 → 112
Log AUC_{last}	Sequence	0.002	
	Volunteer (sequence)	0.0001	
	Period	0.6	
	Treatment (Genotropin® vs EP2000)	0.7	92 → 106

Figure 6: NEFA serum concentrations after subcutaneous injection of EP2000 and Genotropin_ (mean _ SD, n = 24)

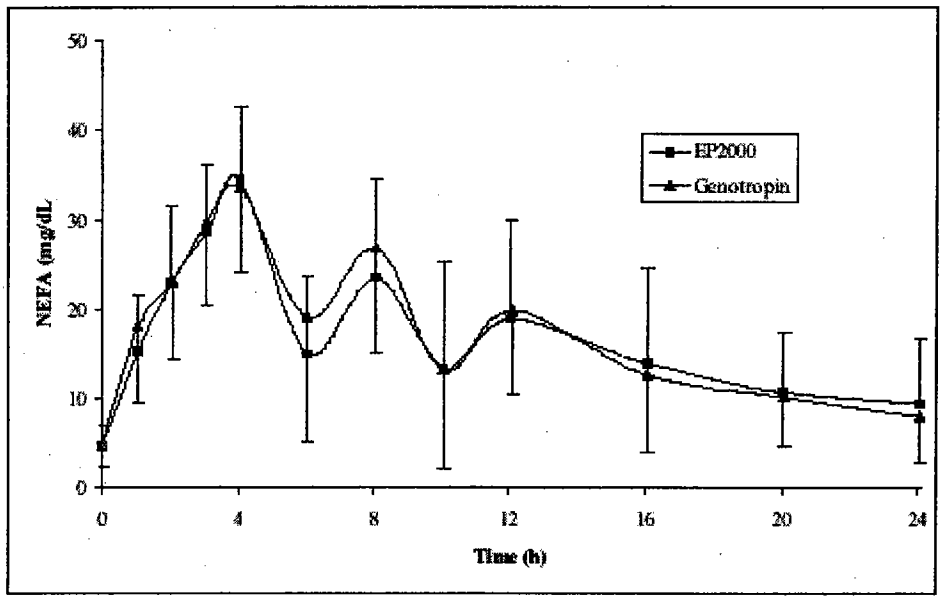

Table 10: Pharmacodynamic response (NEFA) after sc injection of 5 mg of EP2000 and Genotropin

		C_{max} NEFA (mg/dL)	t_{max} NEFA (h)	AUC_{last} NEFA (mg/dL*h)	ΔC_{max} NEFA (mg/dL)	ΔAUC_{last} NEFA (mg/dL*h)
EP2000	Mean	35.5	4	385	30.6	272
	SD	8.0	1	154	7.8	142
	Median	33.5	4	357	29.5	259
	Min	21.7	3	187	18.3	57
	Max	55.4	8	990	48.3	814
Genotropin®	Mean	35.4	6	395	30.7	285
	SD	10.2	3	148	10.1	123
	Median	33.2	4	376	30.4	250
	Min	18.6	3	200	16.6	120
	Max	59.1	12	783	52.0	594
Wilcoxon test (p value)			0.1			

Table 11: Analysis of variance on NEFA log transformed C_{max} and NEFA log transformed
AUC_{last} of EP2000 and Genotropin_ and 90% confidence intervals on the ratio of means

	Effect	Probability	90% Confidence interval
Log C_{max}	Sequence	0.7	
	Volunteer (sequence)	0.1	
	Period	0.5	
	Treatment (Genotropin® vs EP2000)	0.8	92 → 114
Log AUC_{last}	Sequence	0.5	
	Volunteer (sequence)	0.009	
	Period	0.1	
	Treatment (Genotropin® vs EP2000)	0.7	86 → 110

Conclusion:

This study demonstrated that the 5 mg lyophilized formulation of Omnitrope (EP2000) developped by Biochemie GmbH is pharmacokinetically (GH Cmax, AUCinf and tmax) and pharmacodynamically (IGF-1, IGFBP-3, NEFA Cmax, AUClast and tmax) bioequivalent to the 5 mg lyophilized formulation of Genotropin marketed by Pharmacia & Upjohn.

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/s/

Xiao-xiong Wei
8/24/04 08:10:48 AM
BIOPHARMACEUTICS

Hae-Young Ahn
8/24/04 10:03:12 AM
BIOPHARMACEUTICS

9/24/03

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	21-426	Brand Name	Omnitrop
OCPB Division (I, II, III)	DPE II	Generic Name	Somatropin
Medical Division	HFD-510	Drug Class	peptide
OCPB Reviewer	Xiaoxiong (Jim) Wei	Indication(s)	Growth hormone deficiency
OCPB Team Leader	Hae-Young Ahn	Dosage Form	Reconstituted solution
		Dosing Regimen	1.5 mg, 5.8 mg lyophilized powders
Date of Submission	[redacted]	Route of Administration	SC
Estimated Due Date of OCPB Review		Sponsor	Biochemie US, Inc.
PDUFA Due Date	05-31-2003	Priority Classification	1S
Division Due Date			

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	3		
multiple dose:				
Patients-				
single dose:				

multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				

Chronopharmacokinetics				
Pediatric development plan				
Literature References	**17**			
Total Number of Studies				
Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable ?	**Yes**			
Comments sent to firm ?	**Yes**	The major issue is that the sponsor submitted a biowaiver request to claim that Omnitrop 1.5 mg is bioequivalent to Genotropin 1.5 mg. This biowaiver request may not be granted because there is no base to judge the relative bioavailability of Omnitrop 1.5 mg. In order to market Omnitrop 1.5 formulation, a bioequivalence study should be performed.		

Briefing In Content:

The sponsor, Biochemie U.S., Inc. has submitted their NDA for filing under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for Omnitrop®, a recombinant human growth hormone (BC rhGH; EP2000, somatropin/somatotropin). The reference listed drug product is Genotropin®. The sponsor is not seeking AB rating for indications of long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone as well as long-term replacement therapy in adults with GHD of either childhood or adult onset.

The firm has proposed two lyophilized powder dosage forms for subcutaneous injection:

1) Omnitrop 1.5 mg (single use) and

2) Omnitrop 5.8 mg (multiple use) strengths,

The dosage form for Omnitrop 1.5 mg has not been used for any clinical studies. The firm has requested a biowaiver for a bioequivalence claim between Omnitrop 1.5 mg and Genotropin 1.5 mg. The composition of Omnitrop 1.5 mg is not proportional to Omnitrop 5.8 mg formulation (see attachments).

The firm has submitted three Phase 1 pharmacokinetic studies to support clinical pharmacology and biopharmaceutics section. These studies are briefly described as follows:

1) Study EP2K-99-PhISUSA

A Phase I safety study in healthy volunteers to assess the safety, tolerance and pharmacokinetics of EP2000 after single subcutaneous administration

The study objectives were:
a) To assess the safety and tolerance of EP2000 after single dose administration.

b) To assess the pharmacokinetics and pharmacodynamics of EP2000.

c) To validate the pharmacokinetic and pharmacodynamic model to be used in a subsequent Phase I comparative study of EP2000 with Genotropin in order to demonstrate the pharmaceutical equivalence of the two preparations after subcutaneous administration.

2) Study EP2K-99-PhIUSA

A Phase I, double-blind, randomized, 2-way crossover study of EP2000 and Genotropin ® in 24 healthy volunteers after single subcutaneous administration to compare the pharmacokinetics, pharmacodynamics and safety of the two treatments

The study objectives were:
a) To compare the pharmacokinetics of EP2000, a new preparation of r-hGH (test formulation), to that of Genotropin ® (reference formulation), as assessed by a specific immunoassay.

b) To compare the pharmacodynamics of EP2000 with Genotropin ® in terms of IGF-1 serum profile, IGFBP-3 serum profile, and NEFA serum profile.

c) To compare the safety of the test formulation (EP2000) to that of the reference formulation (Genotropin ®).

3) Study EP2K-00-PhIAQ

A Phase I, double-blind, randomised, 2-way cross-over pharmacokinetic study to assess the bioequivalence of EP2000 (lyophilised powder formulation) and EP2000 AQ (liquid formulation) in 24 healthy volunteers after single subcutaneous administration and compare the pharmacodynamics and the safety of the two treatments

The study objectives were:
a) Primary objective was to establish the bioequivalence of the liquid formulation of EP2000 AQ , a new preparation of r-hGH (test formulation) and the lyophilised powder formulation of EP2000 (reference formulation), as assessed by a specific chemiluminescence assay.

b) Secondary objectives were to compare the pharmacodynamics of the liquid formulation of EP2000 AQ with the lyophilised powder formulation of EP2000 in terms of IGF-1, IGFBP-3 and NEFA serum profiles and the safety of the test formulation liquid formulation of EP2000 AQ to that of the reference formulation (lyophilised powder formulation of EP2000) together with 25-hour infusion of 1 mg octreotide (Sandostatin v) to block all endogenous GH-secretions.

Attachments:

1). Studies to support Omnitrop

2). Composition of Omnitrop Formulations

1) Attachment 1: Studies to support Omnitrop

Studies to support Omnitrop

NDA # 21426

	Study #	# of subj	Formulation	Purpose
Phase I	99PHIS USA	12 adults	lyophilized	evaluate the pharmakinetics/pharmakodynamics
	99 PHI USA	24 adults	lyophilized vs Genotropin	bioequivalence of lyophilized vs Genotropin
	00PHI (AQ)	24 adults	lyophilized vs liquid	bioequivalence of lyophilized vs liquid
Clinicals	99 PhIII	89 children	lyophilized vs Genotropin	compare acceleration of growth for lyophilized vs Genotropin, 6 month duration
	00 PhIII Fo	86 children	lyophilized vs Genotropin	compare acceleration of growth for lyophilized vs Genotropin, 3 month duration
	00 PhIII AQ	86 children	lyopilized vs liquid	compare acceleration of growth for lyophilized vs liquid, 6 months

The same children participated in all three clinical studies (except 3 dropouts).
These studies ran consecutively for 15 months.

Composition of the Pharmaceutical form of Omnitrop 1.5 mg

Ingredient	Amount per vial	Function
Active ingredient		
Recombinant Somatropin	1.5 mg (4.5 IU)	Active substance
Other ingredients		
[redacted]		
[redacted]		
Glycine	27.6 mg	Isotonicity and bulking agent
[redacted]		
Water for Injection	[2]	Solvent

[1] Including the phosphate from the BC r-hGH bulk solution.

Composition of the pharmaceutical form of OMNITROP® 5.8 mg

Ingredient	Amount per vial	Function
Active ingredient		
Recombinant Somatropin	5.8 mg (17.4 IU)	Active substance
Other ingredients		
[redacted]		
[redacted]		
Glycine	*27.6 mg*	*Isotonicity and bulking agent*
[redacted]		
Water for Injection	[2]	Solvent

[1] Including the phosphate from the BC r-hGH bulk solution.

Inactive ingredients	Omnitrop 1.5	Genotropin 1.5	Omnitrop 5.8	Genotropin 5.8
Sodium dihydrogen phosphate anhydrous	[redacted]	0.3 mg	[redacted]	0.32 mg
Disodium hydrogen phosphate anhydrous	[redacted]	0.3 mg	[redacted]	0.31 mg
Glycine	27.6 mg	27.6 mg	27.6 mg	2.2 mg
Mannitol	N/A	N/A	N/A	1.8 mg
[redacted]				
Solvent (diluent vial or rear chamber	1.0 ml WFI	1.0 ml WFI	1.0 ml WFI, 1.5 % Benzyl alcohol	1 ml WFI, 0.3% m-Cresol (preservative) 45 mg Mannitol
			Omnitrop 5.8 and Genotropin 5.8 have been demonstrated to be bioequivalent.	

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/s/

Xiao-xiong Wei
9/24/03 10:16:34 AM
BIOPHARMACEUTICS

Hae-Young Ahn
9/24/03 11:06:14 AM
BIOPHARMACEUTICS

3.11.02

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-426	Brand Name	Omnitrop
OCPB Division (I, II, III)	DPE II	Generic Name	Somatropin
Medical Division	HFD-510	Drug Class	peptide
OCPB Reviewer	Xiaoxiong (Jim) Wei	Indication(s)	Growth hormone deficiency
OCPB Team Leader	Hae-Young Ahn	Dosage Form	Reconstituted solution
		Dosing Regimen	1.5 mg, 5.8 mg lyophilized powders and 5.0 mg/1.5 liquid
Date of Submission	12-31-01	Route of Administration	SC
Estimated Due Date of OCPB Review	N/A	Sponsor	Biochemie US, Inc.
PDUFA Due Date	N/A	Priority Classification	N/A
Division Due Date	N/A		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	3		
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	3		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	17			
Total Number of Studies				

Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable ?	**No.**	There is a filing issue related to biopharmaceutics. Based on submission and the confirmation back from the sponsor, drug substances used in clinical pharmacology and phase 3 clinical studies were made in USA. However, the to-be-marketed drug substance will be produced in Kundl, Austria. There is a lack of bridging study between these two drug substances.		
Comments sent to firm ?		1). There is a filing issue related to biopharmaceutics. On Section 03 / 0002 (Volume 25), it clearly indicated that drug substances used in clinical pharmacology and phase 3 clinical studies were made in USA. However, the to-be-marketed drug substance will be produced in Kundl, Austria. Beth Brannan at Geneva Phamraceuticals confirmed this issue on Feb. 22, 2002. If this is the case, a pharmamacokinetic study should be conducted to bridge these two drug substances made in two different locations. 2). The other major issue other than filing issues is that the sponsor submitted a biowaiver request for Omnitrop 1.5 mg lyophilized powder. This biowaiver request may not be granted because the formulation for low strength of Omnitrop 1.5 mg lyophilized powder ***is NOT*** proportional in composition to 5.8 mg formulation.		
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

Briefing In Content:

The sponsor, Biochemie U.S., Inc. has submitted their NDA for filing under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for Omnitrop®, a recombinant human growth hormone (BC rhGH; EP2000, somatropin/somatotropin). The reference listed drug product is Genotropin®. The sponsor is seeking AB rating for indications of long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone as well as long-term replacement therapy in adults with GHD of either childhood or adult onset.

Omnitrop® is presented in two dosage forms for subcutaneous injection, Omnitrop, lyophilizates to be reconstituted (available in two strengths), and Omnitrop Liquid and in three drug products:

(1). Lyophilized powder for solution for injection;

- Omnitrop 1.5 mg (single use) and

- Omnitrop 5.8 mg (multiple use) strengths,

(2). Liquid formulation for injection, Omnitrop Liquid, 5 mg / 1.5 ml (multiple use).

During development of Omnitrop, Biochemie directly compared its lyophilized product to the Reference Listed Drug Genotropin® from Pharmacia & Upjohn. Three clinical pharmacology studies, EP2K-99-PhISUSA, EP2K-99-PhIUSA and EP2K-00-PhI(AQ), were performed in healthy volunteers at the single dose of 5 mg administered subcutaneously. The endogenous hGH secretion was suppressed by a continuous IV infusion of octreotide in order to mimic growth hormone deficiency. The aim of study EP2K-99-PhIUSA was to establish bioequivalence between Omnitrop 5.8mg lyophilized formulation to that of Genotropin®. The study EP2K-00-PhI(AQ) was to establish bioequivelence between Omnitrop 5.8mg lyophilized formulation and Omnitrop 5 mg/1.5ml liquid formulation.

For Omnitrop 1.5 mg lyophilized formulation, the sponsor has requested a biowaiver status.

Attachments:

1). Studies to support Omnitrop

2). Composition of Omnitrop Formulations

---

1) Attachment 1: Studies to support Omnitrop

Studies to support Omnitrop

NDA # 21426

	Study #	# of subj	Formulation	Purpose
Phase I	99PHIS USA	12 adults	lyophilized	evaluate the pharmakinetics/pharmakodynamics
	99 PHI USA	24 adults	lyophilized vs Genotropin	bioequivalence of lyophilized vs Genotropin
	00PHI (AQ)	24 adults	lyophilized vs liquid	bioequivalence of lyophilized vs liquid
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	00 PhIII Fo	86 children	lyophilized vs Genotropin	compare acceleration of growth for lyophilized vs Genotropin, 3 month duration
	00 PhIII AQ	86 children	lyopilized vs liquid	compare acceleration of growth for lyophilized vs liquid, 6 months

The same children participated in all three clinical studies (except 3 dropouts).
These studies ran consecutively for 15 months.

Attachment 2: Composition of Omnitrop Formulations

Composition of the Pharmaceutical form of Omnitrop 1.5 mg

Ingredient	Amount per vial	Function
Active ingredient		
Recombinant Somatropin	1.5 mg (4.5 IU)	Active substance
Other ingredients		
[redacted]		
[redacted]		
Glycine	27.6 mg	Isotonicity and bulking agent
[redacted]		
Water for Injection	[2]	Solvent

[1] Including the phosphate from the BC r-hGH bulk solution.

Composition of the pharmaceutical form of OMNITROP® 5.8 mg

Ingredient	Amount per vial	Function
Active ingredient		
Recombinant Somatropin	5.8 mg (17.4 IU)	Active substance
Other ingredients		
[redacted]		
[redacted]		
Glycine	*27.6 mg*	*Isotonicity and bulking agent*
[redacted]		
Water for Injection	[2]	Solvent

[1] Including the phosphate from the BC r-hGH bulk solution.

Inactive ingredients	Omnitrop 1.5	Genotropin 1.5	Omnitrop 5.8	Genotropin 5.8
Sodium dihydrogen phosphate anhydrous	[redacted]	0.3 mg	[redacted]	0.32 mg
Disodium hydrogen phosphate anhydrous	[redacted]	0.3 mg	[redacted]	0.31 mg
Glycine	27.6 mg	27.6 mg	27.6 mg	2.2 mg
Mannitol	N/A	N/A	N/A	1.8 mg
[redacted]				
Solvent (diluent vial or rear chamber	1.0 ml WFI	1.0 ml WFI	1.0 ml WFI, 1.5 % Benzyl alcohol	1 ml WFI, 0.3% m-Cresol (preservative) 45 mg Mannitol
			Omnitrop 5.8 and Genotropin 5.8 have been demonstrated to be bioequivalent.	

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/s/

Xiao-xiong Wei
3/4/02 01:08:41 PM
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Hae-Young Ahn
3/11/02 11:39:29 AM
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