CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-905

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21-905	Submission Date: 11/30/2005
Brand Name	Valtropin®
Generic Name	Somatropin [rDNA origin] for injection
Reviewer	Xiaoxiong (Jim) Wei, M.D., Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCP Division	Division of Clinical Pharmacology II
ORM division	Division of Metabolic and Endocrine Products
Sponsor	LG Life
Relevant IND(s)	62,376
Submission Type; Code	Original
Formulation; Strength(s)	5.0 mg lyophilized powder
Dosing regimen	For pediatric patients with growth hormone deficiency (GHD), the recommended dosage is 0.023 - 0.043 mg/kg body weight/day, 6-7 times a week, given by subcutaneous injection. For children with turner syndrome, the recommended dosage is up to 0.054 mg/kg body weight/day, 6-7 times a week, given by subcutaneous injection. For adult hGH-deficient patients, the recommended dosage at the start of therapy is 0.33 mg/day (equivalent to 0.005 mg/kg/day) given as a subcutaneous injection. The dosage is gradually increased but not more than 0.66 mg/day (equivalent to 0.010 mg/kg/day) after 4 weeks depending upon patient's tolerance of treatment.
Proposed Indication	[redacted] b(4)

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1. EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS

From the Clinical Pharmacology standpoint, the application is acceptable to market 5.0 mg Valtropin. This recommendation and labeling comments should be conveyed to the sponsor as appropriate.

1.2 Phase IV

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Valtropin® [somatropin (rDNA origin) for injection] is a protein hormone of recombinant DNA origin. The hormone is produced by recombinant DNA technology in yeast cells *(Saccharomyces cerevisiae)*. Valtropin® has 191 amino acid residues and a molecular weight of 22,125 daltons. The amino acid sequence of the product is identical to that of human growth hormone (hGH) of pituitary origin. Valtropin® is a lyophilized powder in 5-mg strength (15 IU) intended for subcutaneous injection after reconstitution.

A comparable drug product, Eutropin™ INJ with 1.33-mg (4 IU) strength, containing the same drug substance, has been marketed in Korea since 1993 for hGH replacement therapy in pediatric patients with GHD. In 1998, the drug was approved for treatment of children with Turner's syndrome, and in 2003 for GHD in adults in Korea.

To support marketing their growth hormone products in US, the sponsor developed new 5-mg strength with a new brand name of Valtropin with three new clinical studies, one pharmacokinetic study and two clinical efficacy trials.

In a double-blind, randomized, single dose study in 24 healthy volunteers, Valtropin® was crossed over to a marketed comparator, Humotrope to evaluate the relative bioavailability. Subcutaneous administration of 0.073 mg/kg body weight of Valtropin® versus (vs) comparator resulted in a mean maximum serum concentration (C_{max}) of 43.97 ng/mL vs 38.64 ng/mL and an area under the curve (AUC_{0-24h}) of 369.90 ng·hr/mL vs 337.50 ng·hr/mL. C_{max} was reached at 4.00 hr versus 5.00 hr and terminal elimination half-life was 3.03 hr vs 3.12 hr. The study was performed without endogenous growth hormone suppression. PK analysis was conducted with baseline correction.

Serum concentrations of human growth hormone were analyzed by [redacted] : of the 22,000 MW form of human growth hormone in human serum. b(4)

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?

Valtropin® [somatropin (rDNA origin) for injection] is a protein hormone of recombinant DNA origin. The hormone is produced by recombinant DNA technology in yeast cells *(Saccharomyces cerevisiae)*. Valtropin® has 191 amino acid residues and a molecular weight of 22,125 daltons. The amino acid sequence of the product is identical to that of human growth hormone (hGH) of pituitary origin. Valtropin® is a lyophilized powder intended for subcutaneous injection after reconstitution. A pre-filled syringe of 1.5 mL clear solution solvent is provided for reconstitution of the powder. After reconstitution with 1.5 mL solvent the solution contains 3.33 mg/mL of somatropin.

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.

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.

Proposed Indications:

Pediatric Patients:

- [redacted]

b(4)

- [redacted]

Adult Patients:

[redacted]

Proposed Dosage Recommendation

- Growth hormone deficiency in children

The recommended dosage is 0.023 - 0.043 mg/kg body weight/day, 6-7 times a week, given by subcutaneous injection.

- Children with Turner Syndrome

The recommended dosage is up to 0.054 mg/kg body weight/day, 6-7 times a week, given by subcutaneous injection.

- Adult patients with growth hormone deficiency

The recommended dosage at the start of therapy is 0.33 mg/day (equivalent to 0.005 mg/kg/day) given as a subcutaneous injection. The dosage is gradually increased but not more than 0.66 mg/day (equivalent to 0.010 mg/kg/day) after 4 weeks depending upon patient's tolerance of treatment.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the pharmacokinetic profiles of Valtropin following a single subcutaneous administration in healthy adult subjects?

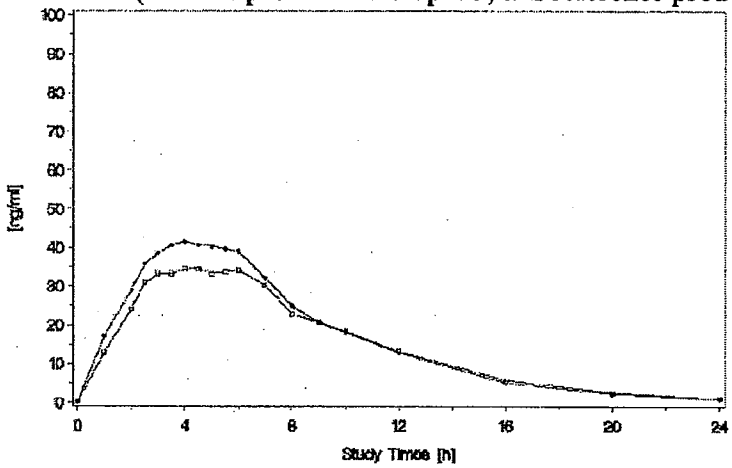
In a double-blind, randomized, single dose study in 24 healthy volunteers, Valtropin® was crossed over to a marketed comparator, Humotrope to evaluate the relative bioavailability. Subcutaneous administration of 0.073 mg/kg body weight of Valtropin® versus (vs) comparator resulted in a mean maximum serum concentration (C_{max}) of 43.97 ng/mL vs 38.64 ng/mL and an area under the curve (AUC_{0-24h}) of 369.90 ng·hr/mL vs 337.50 ng·hr/mL. C_{max} was reached at 4.00 hr versus 5.00 hr and terminal elimination half-life was 3.03 hr vs 3.12 hr. It was demonstrated that Valtropin® shows a relative bioavailability comparable to a marketed product, Humotrope. In order to measure baseline of growth hormone, 4 basal determinations were performed on the previous day (-24, -16, -8h) and approximately 30 min prior to administration and serum samples were collected at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 12, 16, 20 and 24 h post administration. Results are summarized in Table 1 and Figure 1. The major weakness of the study is that the sponsor did not conduct pharmacodynamic analysis, which is typically done simultaneously with PK analysis in growth hormone drug applications.

Table 1: Mean results of pharmacokinetic parameters

	Valtropin™	Comparator product	Ratio Valtropin™ vs comparator product®	90% CI
Parameter	Geom. mean (%CV)	Geom. mean (%CV)		
$AUC_{0-\infty}$ (ng·h/ml)	377.90 (24.0%)	345.30 (25.2%)	109.45%	102%-118%
AUC_{0-24} (ng·h/ml)	369.90 (26.0%)	337.50 (26.4%)	109.59%	101%-119%
C_{max} (ng/ml)	43.97 (44.9%)	38.64 (39.4%)	113.78%	97%-133%
t_{max} (h)*	4.00 (2.5-6)	5.00 (2.5-7)	-0.5 h#	-1 h, ±0 h
$t_{1/2}$ (h)	3.03 (41.0%)	3.12 (40.7%)	-	-

* median and range; # difference

Figure 1: Mean serum concentration-time profiles of somatropin after baseline correction (o-o test product Valtropin®, □-□ reference product Humotrope®)



Reviewer's comments:

If healthy adult subjects are used in this type of bioavailability study, the endogenous growth hormone should be suppressed by continuous intravenous administration of octreotide at a rate of 0.04 mg/hour, which simulates a condition of growth hormone deficiency. The sponsor conducted this BA/BE study in healthy adult subjects without endogenous growth hormone suppression. The sponsor measured 4 time during 24 hours period at predose (-24, -16, -8, -0.5 hr) and made an average of 4 measurements as the baseline and assumed at 0 hours as zero concentrations and the rest of concentrations minus the baseline as the baseline corrected concentrations used to analyze PK parameters. Although the endogenous growth hormone was not suppressed, the endogenous growth hormone in healthy adult subjects with ages of 40 – 55 years was in very low range (below 0.3 ng/mL in more that 80% of the subjects). A single bolus subcutaneous injection of 5-mg exogenous growth hormone was overwhelmingly dominant in serum. Therefore, the study design and analysis are acceptable.

The results in PK parameters demonstrate that Valtropin and Humotrope are comparable though Cmax did not meet 90% CI acceptance criteria. The major weakness of the study is that the sponsor did not conduct pharmacodynamic analysis, which is typically done simultaneously with PK analysis in growth hormone drug applications.

2.3 GENERAL BIOPHARMACEUTICS

A comparable drug product, Eutropin™ INJ, containing the same drug substance, was granted marketing authorization in Korea in 1993 for hGH replacement therapy in pediatric patients with GHD. In 1998, the drug was approved for treatment of children with TS, and in 2003 for GHD in adults in Korea. In Eutropin™ 4 IU INJ a quantitatively different formulation is used (Table 2).

Table 2: Composition of Eutropin™ INJ and Valtropin™

Regulatory Status		MA in Korea		Submitted for MA in USA and EU	
Drug Product Name		Eutropin™ INJ		Valtropin™	
Composition		4 IU Formulation		15 IU Formulation	
	Function	Per vial	Weight ratio	Per vial	Weight ratio
Active ingredient					
Somatropin	drug substance	1.33 mg		5.00 mg	
Excipients					
Mannitol	bulking agent	5.00 mg		45.00 mg	
Glycine	stabiliser	20.00 mg		10.00 mg	
Sodium phosphate buffer, dibasic	buffer	ca. 1.35 mg		2.98 mg	
Sodium phosphate buffer, monobasic	buffer	-		0.22 mg	

MA Marketing authorisation; 1 N sodium hydroxide and 1 N hydrochloric acid are used to adjust pH

b(4)

Originally, Eutropin™ was proposed for use as the brand name, and thus Valtropin™ is referred to as Eutropin™ in the reports of the three clinical studies (BP-EU-001, BP-EU-002, and BP-EU-003. In order to avoid confusion, the 15 IU formulation of somatropin proposed for marketing in USA and Europe is from now on always referred to as Valtropin™, whereas the 4 IU formulation authorized in Korea is always referred to as Eutropin™ INJ. Using 5.0-mg Valtropin formulation, three new clinical studies (one PK study in healthy adult subjects and two clinical trials in pediatric patients) were conducted to support this application to market Valtropin in US market (Table 3).

Table 3: International clinical studies performed with Valtropin®

	Valtropin™: 15 IU Formulation		
	Study code	Study drug	Comments
Bioavailability study	BP-EU-001 [5.3.1.2.1]	*Batch:* MGH006	Randomised, double-blind, cross-over, comparator-controlled Phase I study Somatropin-containing comparator product: 24 healthy male adults
GHD in children	BP-EU-003 [5.3.5.A.1.1]	MGH005 MGH006 MGH002*	Multicentre, multinational, double-blind, randomised, comparator-controlled Phase III study Somatropin-containing product used as active control: 147 patients
Children with Turner syndrome	BP-EU-002 [5.3.5.B.2.1]	MGH003 MGH002*	Single-centre, open-label, randomised Phase III study (historical controls) 30 patients

There is no PK bridge study between Valtropin 15 IU and Eutropin 4 IU. For adult growth hormone deficiency (GHD), the clinical trials were all conducted with Eutropin 4 IU. Valtropin was not used in the adult GHD indication. However, the sponsor is seeking approval the adult GHD indication as well. The pediatric GHD studies were conducted using both formulations, Valtropin for the new trial [BP-EU-003] and Eutropin for the original trial in Korea. For Turner's syndrome, the new trial in Russia was

conducted with Valtropin and also a Korean trial was conducted with Eutropin 4 IU formulation. Because the clinical outcomes are comparable from these two different formulations in different clinical trials, these clinical trials can be considered as clinical bridge studies between these two formulations.

2.4 ANALYTICAL

Serum concentrations of human growth hormone were analyzed by means of a commercially available [redacted]

b(4)

[redacted] The fluorescence of each sample is proportional to the amount of hGH present in the sample. Validation data is summatized in Table 4.

Table 4. Assay validation results for serum samples

Precision (%CV)	<1.64% within assays
	<5.1% between assays
Accuracy	96.67 – 103.33%
Linearity	0.038 – 40.0 ng/mL
Sensitivity	LOQ: 0.038 ng/mL
Specificity	Cross reactivity from serum hLH, hPL, hFSH, hGH 20kD, hTSH [redacted]

b(4)

3 DETAILED LABELING RECOMMENDATIONS

LABELING COMMENTS:

(~~Strikeout text~~ should be removed from labeling; underlined text should be added to labeling)

b(4)

1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

4 APPENDICES

4.1 OCP FILING MEMO

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
	Information		Information
NDA Number	21-905	Brand Name	Valtropin®
OCPB Division (I, II, III)	DPE II	Generic Name	Somatropin (rDNA origin) for injection
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
		Strength	5.0 mg (15 IU) lyophilized powders
Date of Submission	11-30-2005	Route of Administration	SC
Estimated Due Date of OCPB Review		Sponsor	LG Life Sciences
PDUFA Due Date		Priority Classification	S1
ion 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) -				
4.2 Healthy Volunteers-				
single dose:	**X**	**1**		
multiple dose:				
4.2.1 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				
Total Number of Studies				

lability and QBR comments		
4.2.1.2	**"X" if yes**	1 Comments
ication filable ?	**Yes**	
ments sent to firm ?	**Yes**	

Submission:

LG Life Sciences, via their US agent PAREXEL has submitted a NDA for Valtropin® [somatropin (rDNA origin)] for daily injection. Valtropin® is proposed for [redacted] b(4)

[redacted] b(4)

Valtropin™ is ar [redacted] drug product of recombinant human growth hormone (rhGH), manufactured in genetically engineered yeast cells (*Saccharomyces cerevisiae*). The drug substance somatropin has 191 amino acid residues with a molecular formula of C990H1528N262O300S7 and a molecular weight of 22,125 Daltons. The drug product is a white or almost white powder and results in a clear solution after reconstitution in aqueous solvents.

An early version of Valtropin®, Eutropin™ INJ (a 1.33 mg / 4 IU formulation of somatropin initially approved for marketing in Korea) has gained regulatory approval in 12 countries worldwide.

This NDA contains one clinical pharmacology study:

Study BP-EU-001: A two-period, double-blind, randomized, single subcutaneous dose, cross-over study in twenty-four healthy male volunteers to investigate the bioavailability of two different recombinant human growth hormone preparations (Valtropin® versus European Humatrope®)

This NDA includes clinical data from the following four completed clinical studies involving approximately 284 patients (189 children, 95 adults) to support the proposed labeling for Valtropin®:

Study BP-EU-003; a randomized, controlled, double-blind, 12-month, multi-center (Europe), Phase III clinical study of Eutropin™ (now filed under the trade name Valtropin®) against an active control in 149 treatment-naive children with GHD (149 patients [99 versus 50] randomized; 147 patients [98 versus 49] safety population; 129 patients [88 versus 41] full analysis set).

Study HGCL-001; a randomized, placebo-controlled, double-blind, multi-center (Korea), Phase III clinical study of Eutropin™ INJ administered over a duration of 3-6 months in 95 adults with GHD (95 patients randomized; 92 patients treated, ITT population, safety population).

Study BP-EU-002; an uncontrolled, open, single-center (Moscow) 12-month Phase III clinical study of Eutropin™ INJ (now filed under the trade name Valtropin®) in 30 girls with Turner Syndrome (30 patients full analysis set, safety analysis set).

Study TS-KOR-06102005; an uncontrolled, open, multi-center (Korea) 12-month Phase III clinical study of Eutropin™ INJ in 60 girls with Turner Syndrome (60 patients enrolled and analyzed for safety; 50 patients analyzed for efficacy).

The serum concentrations of Valtropin® were measured via a _____ b(4)
_____ An assay validation study is included in the submission.

4.2 Proposed Package insert (separate file)

4.3 Individual Study Review

SYNOPSIS

Study BP-EU-001

Name of Sponsor/Company: BioPartners S.A.
Name of Finished Product:

Test drug: Somatropin BioPartners (Eutropin™)
Reference drug: European Humatrope®
Name of Active Ingredient: Somatropin

Title of Study: A Two-Period, Double-Blind, Randomized, Single Subcutaneous Dose, Cross-Over Study in Twenty-Four Healthy Male Volunteers to Investigate the Bioavailability of Two Different Recombinant Human Growth Hormone Preparations (Somatropin BioPartners versus European Humatrope®)

Investigator(s):
"Leiter der klinischen Prüfung" according to § 40 German Drug Law (Principal Investigator):
Michael Lissy, Physician
For a list and description of investigators and other important participants in the study, including their role in the study and brief CVs please refer to Appendix 16.1.4.

Study centre: [redacted] b(4)

Publication (reference): Not applicable to the present report

Studied period:
date of first enrolment: 30 Sep. 02
date of last completed: 11 Nov. 02

Phase of development: Phase I

Objectives:
The primary objective of this study was to evaluate the bioavailability and pharmacokinetic parameters of two somatropin formulations in healthy subjects. Secondary objective was the evaluation of the tolerability and safety of these formulations.

Primary variables: area under the curve (AUC(0-∞)), maximal concentration (Cmax) after baseline-correction, time of maximum (tmax).

Main secondary variables:
Area under the curve (AUC0-24) and terminal half-life (t½) of somatropin after baseline-correction

Safety variables:
Vital signs (blood pressure, heart rate, body temperature), local tolerability, physical examination, laboratory parameters, ECG recording, adverse events throughout the study

Methodology:
Double-blind, cross-over, randomized, single-dose, bioavailability study

Number of subjects (planned and analyzed):
Number of subjects planned: 24
Number of subjects analyzed: 24

Diagnosis and main criteria for inclusion:
Healthy male Caucasian subjects, age between 40 and 55 years, non-smokers or smokers of less than 10 cigarettes per day.

Name of Active Ingredient: Somatropin

Test drug, dose and mode of administration, batch number:
Injectable solution of Somatropin BioPartners (Eutropin™), 0.073 mg/kg body weight administered as single subcutaneous injections, batch number: MGH 006 Somatropin BioPartners (Eutropin™) MGD 001 (solvent for Somatropin BioPartners (Eutropin™))

Duration of treatment: Two times single dose

Reference drug, dose and mode of administration, batch number:
Injectable solution of European Humatrope® , 0.073 mg/kg body weight administered as single subcutaneous injections, batch number: FF1A69T (European Humatrope®) FF1C27E (Solvent for European Humatrope)

Criteria for evaluation:

Efficacy:
Not applicable to the present study

Pharmacodynamics: Not applicable to the present study

Pharmacokinetics:
AUC0-∞, AUC0-24, Cmax and tmax of baseline-corrected serum concentrations of somatropin were compared statistically between treatments, other pharmacokinetic parameters were evaluated descriptively only.

Safety:

Adverse events, vital signs (blood pressure, heart rate, body temperature), local tolerability, physical examination, laboratory parameters, ECG recording pre-study and post-study only

Statistical methods:
Analysis of variance with sequence, subject within sequence, period and treatment effects applied to AUC0-24, AUC0-□, and Cmax after logarithmic pre-transformation. Estimation of ratios test/reference with 90% confidence intervals. The pre-defined acceptance range was 0.8-1.25 for AUC and 0.7-1.43 for Cmax. tmax was compared between treatments on the original, untransformed scale by the corresponding nonparametric methods.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS: Not applicable to the present study

PHARMACODYNAMIC RESULTS:

Not applicable to the present study

PHARMACOKINETIC RESULTS:

Over 80% of the 24 subjects exhibited baseline levels below 0.3 ng/ml, the maximum baseline ever observed was 1.58 ng/ml. Maximal measured concentrations ranged from 13.5 to 82.2 ng/ml and thus clearly exceeded the baseline.

Mean concentration-time curves (see Section 14.2.2) were similar in shape for both treatments, but on a slightly higher level for the test preparation. They were almost flat (with only low fluctuation) between about 3h and 6h after dosing. Maximal concentrations were reached between 2.5 and 7 hours after dosing. From about 9 h p.a. onwards the mean baseline-corrected concentration-time curves were 04-May-04/REP.MA185.003.doc/ML/ob CONFIDENTIAL page 4 of 69 Name of practically indistinguishable and decreased with a half-life of about 3 hours.

The relative bioavailability of Eutropin (Somatropin BioPartners) in relation to European Humatrope was estimated at 109.5% based on AUC0-□and AUC0-24 with 90% confidence that ranged between 101% and 119%. The test/reference ratio was estimated at 113.8% for Cmax with (97%, 133%) as confidence interval.

SAFETY RESULTS:

A total of 44 post-dose adverse events occurred in the course of the trial. Twenty one post-dose adverse events were seen in 14 subjects during test treatment (Eutropin, injectable solution of Somatropin BioPartners, 0.073 mg/kg body weight). Twenty three post-dose adverse events were seen in 13 subjects during reference treatment (European Humatrope, injectable solution of somatropin, 0.073 mg/kg body weight). All presented

adverse events had resolved at the end of the trial. No serious or other significant adverse events occurred. As a conclusion both, the test and the reference preparation were well tolerated.

CONCLUSION:

The study was performed according to the study protocol in all important respects. The test preparation (Eutropin) and the reference preparation (European Humatrope) were well tolerated. All post-dose adverse events were of mild or moderate (once only) intensity. No severe adverse events appeared. All drug related adverse events resolved before the end of the study. There was no significant difference in adverse events between the treatment groups. The 90% confidence intervals for the AUC0-□-ratio and the AUC0-24-ratio and the Cmax-ratio fell entirely within the pre-defined acceptance criteria. It can therefore be concluded that Eutropin (Somatropin BioPartners) and European Humatrope are bioequivalent.

Date of the report: 04-May-2004

Figure 1. Mean serum concentration-time profiles

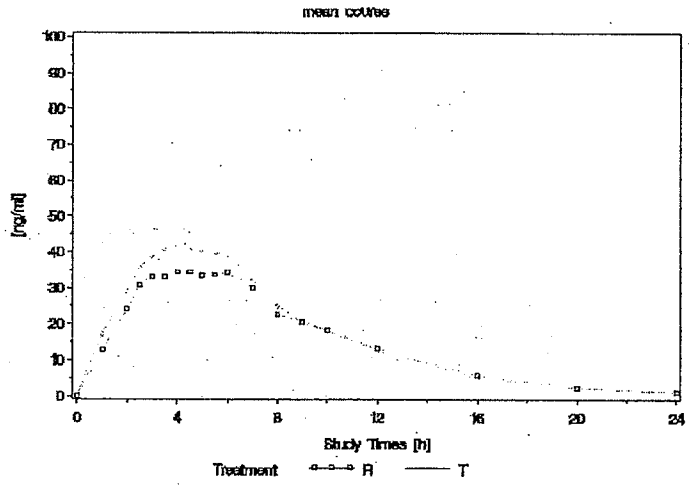


Table 1: Mean results of pharmacokinetic parameters

	Valtropin™	Comparator product	Ratio Valtropin™ vs comparator product[@]	90% CI
Parameter	Geom. mean (%CV)	Geom. mean (%CV)		
$AUC_{0-\infty}$ (ng·h/ml)	377.90 (24.0%)	345.30 (25.2%)	109.45%	102%-118%
AUC_{0-24} (ng·h/ml)	369.90 (26.0%)	337.50 (26.4%)	109.59%	101%-119%
C_{max} (ng/ml)	43.97 (44.9%)	38.64 (39.4%)	113.78%	97%-133%
t_{max} (h)*	4.00 (2.5-6)	5.00 (2.5-7)	-0.5 h[#]	-1 h, ±0 h
$t_{1/2}$ (h)	3.03 (41.0%)	3.12 (40.7%)	-	-

[@] median and range; [#] difference

Table 4. Summary of mean serum concentrations of somatropin after baseline correction (ng/mL), (R: European Humatrope, 0.073mg/kg body weight; T: Eutropin, inj. 0.073 mg/kg n=body weight)

Treatment T

Sampling Time	N	Mean	Std Dev	Minimum	Maximum	%CV
base-line	24	0.24	0.37	.000	1.58	157.1
predose	24	0.00	0.00	.000	.000	.
1h	24	17.12	5.13	9.44	29.5	30.0
2h	24	28.93	13.21	8.40	58.3	45.7
2h30min	24	35.74	15.99	8.11	66.8	44.7
3h	24	38.59	15.47	11.1	68.1	40.1
3h30min	24	40.64	16.63	9.70	72.1	40.9
4h	24	41.54	16.14	10.2	73.8	38.9
4h30min	24	40.65	16.17	10.0	82.2	39.8
5h	24	40.30	14.62	11.3	76.4	36.3
5h30min	24	39.66	13.98	12.1	70.5	35.3
6h	24	36.99	15.18	13.4	80.6	36.9
7h	24	32.16	11.83	12.5	59.2	36.8
8h	24	24.94	8.67	10.6	44.0	34.8
9h	24	20.63	6.15	11.2	31.6	29.8
10h	24	16.66	5.92	8.52	30.4	32.8
12h	24	12.67	4.96	6.04	23.9	38.5
16h	24	5.08	2.63	1.31	11.8	51.9
20h	24	2.20	1.61	.000	6.51	73.1
24h	24	1.01	1.02	.000	4.01	100.9

Treatment R

Sampling Time	N	Mean	Std Dev	Minimum	Maximum	%CV
base-line	24	0.15	0.19	.020	.710	124.5
predose	24	0.00	0.00	.000	.000	.
1h	24	12.75	5.21	4.96	25.9	40.8
2h	24	24.07	13.38	6.58	57.6	55.6
2h30min	24	30.86	17.29	9.32	71.8	56.0
3h	24	33.09	17.41	9.33	77.5	52.6
3h30min	24	33.15	15.44	9.91	76.9	46.6
4h	24	34.50	16.53	10.0	77.7	47.9
4h30min	24	34.53	16.12	10.5	75.9	46.7
5h	24	33.35	13.24	14.1	68.9	39.7
5h30min	24	33.73	13.00	19.1	69.2	38.5
6h	24	34.17	13.77	18.1	69.5	40.3
7h	24	30.19	11.40	14.4	60.0	37.8
8h	24	22.75	6.83	13.2	43.6	30.0
9h	24	20.66	6.96	10.9	36.1	33.7
10h	24	18.35	5.58	10.8	28.7	30.4
12h	24	13.16	4.16	6.85	21.3	31.6
16h	24	5.74	2.91	2.32	12.7	50.7
20h	24	2.50	1.76	.430	6.85	70.4
24h	24	1.11	1.02	.020	3.93	92.1

Appears This Way
On Original

Table 5. Representative of individual PK data (Subject 1)

Date	Study Day	Treatment	Drug Administration Parameter	Drug Administration Result	Local Tolerability Parameter	Local Tolerability Result	Blood Sampling Parameter	Blood Sampling Result	Weight of Subject	Somatropin Concentration orig. [ng/mL]	Somatropin Concentration baseline corrected [ng/mL]
22OCT1002	Period 1, -24h	T					Clock time (hh:mm)	8:52	0.159	0.11	
							Irrelevant deviation (min)	60			
	Period 1, -16h	T					Clock time (hh:mm)	16:07		0.04	
							Irrelevant deviation (min)	60			
23OCT1002	Period 1, -8h	T					Clock time (hh:mm)	0:07		0.06	
							Irrelevant deviation (min)	60			
	Period 1, -0.5h	T					Clock time (hh:mm)	7:52		0.02	0.00
							Irrelevant deviation (min)	-60			
	Period 1, 0h	T	Clock time (hh:mm)	8:22							0
			Drug received (yes, no)	yes							
			Administration site	Left							
	Period 1, 1h	T					Clock time (hh:mm)	9:22		17	16.7
							Irrelevant deviation (min)	3			
	Period 1, 2h	T					Clock time (hh:mm)	10:07		25	24.7
							Irrelevant deviation (min)	3			
	Period 1, 2.5h	T					Clock time (hh:mm)	10:37		32.7	32.4
							Irrelevant deviation (min)	3			
	Period 1, 3h	T					Clock time (hh:mm)	11:07		39	38.7
							Irrelevant deviation (min)	3			
	Period 1, 3.5h	T					Clock time (hh:mm)	11:37		31.6	31.3
							Irrelevant deviation (min)	3			
	Period 1, 4h	T			Clock time (hh:mm)	12:03	Clock time (hh:mm)	12:07		31.9	31.6
					Erythema	no reddening	Irrelevant deviation (min)	4			
					Edema	no visible reaction					
					Induration (yes, no)	no					
					Pain (yes, no)	no					
					Headache (yes, no)	no					
	Period 1, 4.5h	T					Clock time (hh:mm)	12:37		33.3	33.0
							Irrelevant deviation (min)	4			
	Period 1, 5h	T					Clock time (hh:mm)	13:07		33.6	33.3
							Irrelevant deviation (min)	4			
	Period 1, 5.5h	T					Clock time (hh:mm)	13:37		31.3	31
							Irrelevant deviation (min)	4			
	Period 1, 6h	T					Clock time (hh:mm)	14:07		31.3	31.0
							Irrelevant deviation (min)	4			

Reviewer's comments:

If healthy adult subjects are used in this type of bioavaibility study, the endogenous growth hormone should be suppressed by continuous intravenous administration of octreotide at a rate of 0.04 mg/hour, which simulates a condition of growth hormone deficiency. The sponsor conducted this BA/BE study in healthy adult subjects without endogenous growth hormone suppression. The sponsor measured 4 time during 24 hours period at predose (-24, -16, -8, -0.5 hr) and made an average of 4 measurements as the baseline and assumed at 0 hours as zero concentrations and the rest of concentrations minus the baseline as the baseline corrected concentrations used to analyze PK parameters. Although the endogenous growth hormone was not suppressed, the endogenous growth hormone in healthy adult subjects with ages of 41 – 55 years was in very low range. A single bolus subcutaneous injection of 5-mg exogenous growth hormone was overwhelmingly dominant in serum. Therefore, the study design and analysis are acceptable.

The results in PK parameters demonstrate that Valtropin and Humotrope are bioequivalent though there is no need to establish BE between the two drug products since the sponsor is seeking an approval based on the 505 (b) (1) route. The major weakness of the study is that the sponsor did not conduct pharmacdynamic analysis, which is typically done simultaneously with PK analysis in growth hormone drug applications.

Overall, the sponsor conducted minimal amounts of studies in clinical pharmacology area. With their own data, the labeling contents won't be able to make a standardized format as ADME subsections.

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/s/

Xiao-xiong Wei
9/1/2006 12:49:03 PM
BIOPHARMACEUTICS

Hae-Young Ahn
9/11/2006 12:55:30 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		**Information**
NDA Number	**21-905**	**Brand Name**	**Valtropin®**
OCPB Division (I, II, III)	**DPE II**	**Generic Name**	**Somatropin (rDNA origin) for injection**
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**
		Strength	**5.0 mg (15 IU) lyophilized powders**
Date of Submission	**11-30-2005**	**Route of Administration**	**SC**
Estimated Due Date of OCPB Review	**08-15-2006**	**Sponsor**	**LG Life Sciences**
PDUFA Due Date	**10-01-2006**	**Priority Classification**	**S1**
Division Due Date	**09-01-2006**		

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**	**1**		
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				
Total Number of Studies				

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable?	**Yes**	
Comments sent to firm?	**No**	

Submission:

LG Life Sciences, via their US agent PAREXEL has submitted a NDA for Valtropin® [somatropin (rDNA origin)] for daily injection. Valtropin® is proposed [redacted] b(4)

Valtropin™ is an immediate release drug product of recombinant human growth hormone (rhGH), manufactured in genetically engineered yeast cells (*Saccharomyces cerevisiae*). The drug substance somatropin has 191 amino acid residues with a molecular formula of C990H1528N262O300S7 and a molecular weight of 22,125 Daltons. The drug product is a white or almost white powder and results in a clear solution after reconstitution in aqueous solvents.

An early version of Valtropin®, Eutropin™ INJ (a 1.33 mg / 4 IU formulation of somatropin initially approved for marketing in Korea) has gained regulatory approval in 12 countries worldwide.

This NDA contains one clinical pharmacology study:

Study BP-EU-001: A two-period, double-blind, randomized, single subcutaneous dose, cross-over study in twenty-four healthy male volunteers to investigate the bioavailability of two different recombinant human growth hormone preparations (Valtropin® versus European Humatrope®)

This NDA includes clinical data from the following four completed clinical studies involving approximately 284 patients (189 children, 95 adults) to support the proposed labeling for Valtropin®:

Study BP-EU-003; a randomized, controlled, double-blind, 12-month, multi-center (Europe), Phase III clinical study of Eutropin™ (now filed under the trade name Valtropin®) against an active control in 149 treatment-naive children with GHD (149 patients [99 versus 50] randomized; 147 patients [98 versus 49] safety population; 129 patients [88 versus 41] full analysis set).

Study HGCL-001; a randomized, placebo-controlled, double-blind, multi-center (Korea), Phase III clinical study of Eutropin™ INJ administered over a duration of 3-6 months in 95 adults with GHD (95 patients randomized; 92 patients treated, ITT population, safety population).

Study BP-EU-002; an uncontrolled, open, single-center (Moscow) 12-month Phase III clinical study of Eutropin™ INJ (now filed under the trade name Valtropin®) in 30 girls with Turner Syndrome (30 patients full analysis set, safety analysis set).

Study TS-KOR-06102005; an uncontrolled, open, multi-center (Korea) 12-month Phase III clinical study of Eutropin™ INJ in 60 girls with Turner Syndrome (60 patients enrolled and analyzed for safety; 50 patients analyzed for efficacy).

The serum concentrations of Valtropin® were measured via a [redacted] b(4)
An assay validation study is included in the submission.

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/s/

Xiao-xiong Wei
1/20/2006 11:16:21 AM
BIOPHARMACEUTICS

Hae-Young Ahn
1/20/2006 11:57:17 AM
BIOPHARMACEUTICS