CLINICAL PHARMACOLOGY REVIEW

NDA: 21-538	Submission Date(s): 9 May-06, 21 June-06
Brand Name	Accretropin™
Generic Name	Somatropin, [redacted]
Reviewer	Wei Qiu, Ph.D.
Team Leader (Acting)	Xiao-Xiong (Jim) Wei, Ph.D.
OCP Division	DCPII
OND division	Metabolism and Endocrine Products
Sponsor	Cangene Corporation
Submission Type	Standard; 505(b)(1) submission
Formulation; Strength(s)	Sterile liquid for subcutaneous injection; 5 mg/mL
Indication	[redacted] treatment of pediatric patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone; treatment of short stature associated with Turner syndrome in pediatric patients whose epiphyses are not closed.
Dosage Regimen	*Growth hormone deficiency:* 0.18 to 0.3 mg/kg divided into equal doses given 6 or 7 times per week. *Turner Syndrome:* weekly dosage of up to 0.36 mg/kg divided into equal doses given 6 or 7 days per week.

Table of Contents

1 Executive Summary

Accretropin™ (somatropin, [redacted]) (formally known as [redacted]) is a recombinant human Growth Hormone (rhGH) by recombinant DNA technology in an E.coli expression system. The proposed indications contain [redacted] treatment of pediatric patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone (Growth Hormone

Deficiency) and treatment of short stature associated with Turner syndrome in pediatric patients whose epiphyses are not closed.

This 505(b)(1) submission included the following three clinical studies:

- Study GA-002 compared the bioavailability of Accretropin™ to Humatrope® in Somatostatin suppressed normal, healthy, non-smoking male subjects.
- Study GA-005/5A assessed the safety and efficacy of Accretropin™ for the treatment of short stature in children diagnosed with growth hormone deficiency (GHD) in the dose range of 0.03 to 0.05 mg/kg/day administered subcutaneously 6 times per week.
- Study GA-007/7A assessed safety and efficacy of Accretropin™ for the treatment of short stature in prepubertal children with Turner Syndrome using the dose of 0.06 mg/kg/day subcutaneously 6 times per week.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed this NDA submitted on May 10, 2006 and finds it acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and agency regarding to the language in the package insert. Labeling comments should be conveyed to the sponsor as appropriate.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The point estimates of the geometric mean ratios of Accretropin™ and Humatrope® for hGH AUCt, AUCinf, and Cmax were 94.23%, 96.88%, and 103.84%, respectively. The corresponding 90% confidence intervals were 88.70-100.10% for AUCt, 93.28-100.61% for AUCinf and 95.73-112.63% for Cmax. The mean values of Tmax for Accretropin™ and Humatrope® were 3.83 and 4.40 hours, respectively. The mean half-life values for Accretropin™ and Humatrope® were 3.63 and 3.46 hours, respectively.

Blood levels of IGF-1, IGFBP-3, and glucose were similar following administration of either Accretropin™ or Humatrope®.

2 Question Based Review

2.1 General Attributes of the Drug

1. What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Accretropin™ (somatropin [rDNA origin]; recombinant human growth hormone (rhGH)) is a protein produced by recombinant DNA technology. It is produced during fermentation in E.coli yielding a protein containing 192 amino acids. The N-terminal amino acid, methionine, is later removed to yield a protein that is chemically, immunologically and physicochemically identical to pituitary derived human growth hormone, consisting of 191 amino acids in a single polypeptide chain.

Accretropin™ is presented as a liquid solution containing 1 mL of a 5 mg/mL solution of rhGH (15 IU/mL). **Table 1** outlines the composition of the dosage from.

Table 1. Formulation/Composition of Accretropin™ recombinant human growth hormone

Component	Preclinical/Clinical		Commercial	
	Concentration (in a 1 mL fill vial)	Concentration (as mg/vial)	Concentration (in a 1 mL fill vial)	Concentration (
Pluronic F68	0.2%		0.2%	
Sodium phosphate,				
Sodium phosphate,				
Phenol			0.34%	
Sodium chloride	0.75%		0.75%	
Recombinant human growth hormone (rhGH)	5 mg		5 mg	

Due to the of phenol concentration from (preclinical/clinical studies) batches to 0.34% in the commercial batches, the Agency requested the sponsor to investigate the effect of phenol concentrations on the structure and biological activity during the Pre-NDA meeting. The ONDQA Reviewer, Dr. Yvonne Yang, reviewed and concluded that the pre-clinical and clinical drug substance/drug product and commercial drug substance/drug product are comparable (Please refer to ONDQA review).

2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Somatropin stimulates linear growth in pediatric patients who lack adequate normal endogenous growth hormone.

Accretropin™ (somatropin) is indicated for treatment of pediatric patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone and treatment of short stature associated with Turner syndrome in pediatric patients whose epiphyses are not closed.

3. What are the proposed dosage(s) and route(s) of administration?

The proposed dosage is sterile liquid for subcutaneous injection.

2.2 General Biopharmaceutics

1. What is the relative bioavailability of hGH after administration of Accretropin™ compared to Humatrope® in Somatostatin suppressed normal subjects? What are the levels of IGF-1, IGFBP-3, and glucose after a single dose administration of Accretropin™ or Humatrope®?

A single-dose, double-blind, randomized, two-way crossover study (Study GA-002) was conducted to compare the bioavailability of hGH and levels of IGF-1, IGFBP-3, and glucose after administration of 4 mg Accretropin™ and 4 mg Humatrope® in 24 somatostatin suppressed normal healthy male subjects under fed condition.

Somatostatin suppression of endogenous hGH secretion by an infusion of somatostatin is a commonly used method of analysis of exogenous GH metabolism and elimination, without interference from endogenously produced hGH. In this study, Sandostatin was given for 42 hours at a rate of 25 ug/h, starting from 25 hours prior to drug administration until 17 hours after drug administration.

Accretropin™ (Treatment A) or Humatrope® (Treatment B) was administered as a subcutaneous injection in the abdominal region at 25 hours after the start of an intravenous infusion of Sandostatin, after a standard breakfast. The washout period between hGH administrations in each period was 7 days.

The pharmacokinetic profiles of hGH after administration of Accretropin™ (also known as [redacted] previously) and Humatrope® are presented in **Figure 1**. Pharmacokinetic parameters of hGH are summarized in **Table 2**.

Figure 1. Concentration-time profiles of hGH after administrations of Accretropin™ and Humatrope®

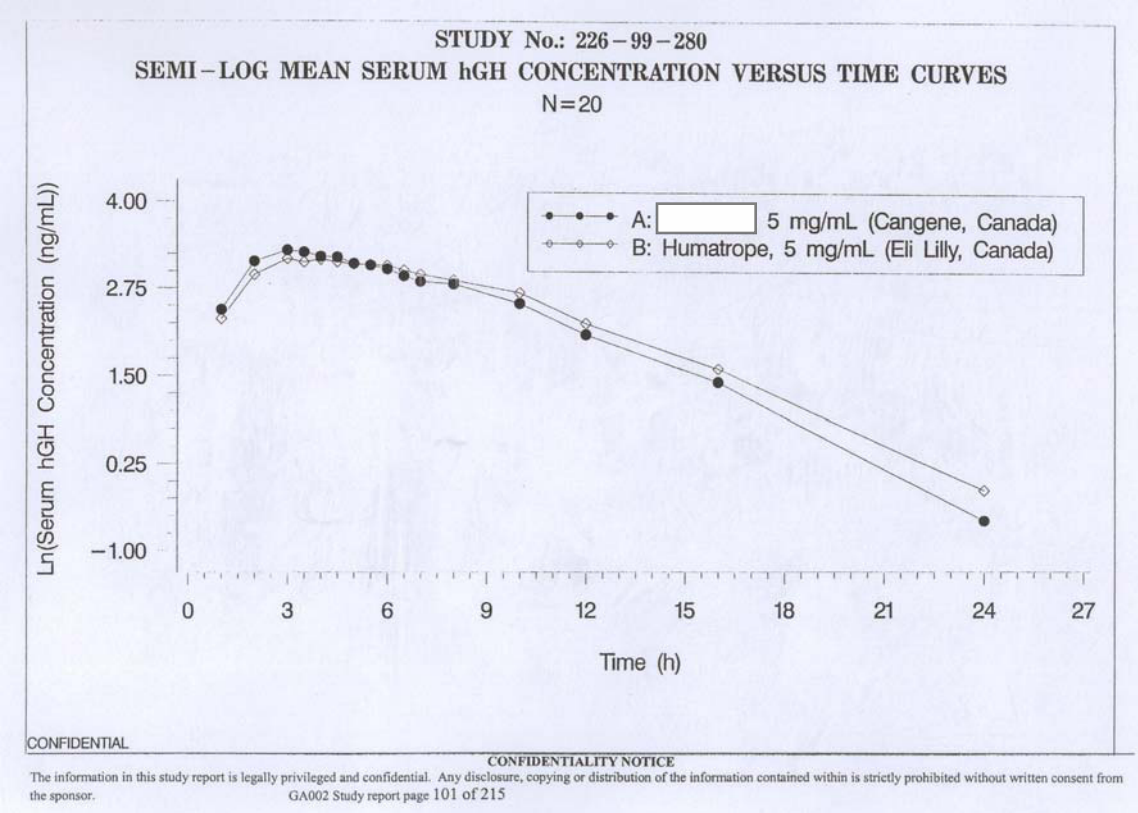

Table 2. Pharmacokinetic parameters of rhGH of Test (Accretropin™) and Reference (Humatrope®) after a single dose

PHARMACOKINETIC RESULTS
(N=20)

(Uncorrected for Measured Drug Content)

Parameter	Test (A)	Reference (B)	Ratio of Geom. Means (%)	90% Geom. Confidence Interval (%)	Intra-Subject CV(%)
	Geometric Mean Arithmetic Mean (CV,%)				
AUC_T (ng·h/mL)	232.93 238.09 (18.53)	247.20 254.09 (18.20)	94.23	88.70 – 100.10	10.80
AUC_I (ng·h/mL)	249.63 255.31 (16.85)	257.67 263.49 (17.38)	96.88	93.28 – 100.61	6.76
C_{max} (ng/mL)	28.18 29.49 (28.23)	27.14 28.24 (24.05)	103.84	95.73 – 112.63	14.52
t_{max}* (hours)	3.50 (1.20)	4.00 (1.37)	-		
λ* (h^{-1})	0.2103 (27.90)	0.2076 (20.28)	-		
$t_{½}$* (hours)	3.63 (36.75)	3.46 (18.21)	-		
* t_{max} is expressed as median (STD), λ and $t_{½}$ are expressed as arithmetic mean (CV,%) only.					

(Corrected for Measured Drug Content)

Parameter	Test (A)	Reference (B)	Ratio of Geometric Means (%)	90% Geom. Confidence Interval (%)
	Geometric Mean			
AUC_T (ng·h /mL)	234.23	243.12	96.35	90.81 – 102.23
AUC_I (ng·h /mL)	251.03	253.42	99.06	95.46 – 102.81
C_{max} (ng/mL)	28.34	26.69	106.17	98.05 – 114.97

The point estimates of the geometric mean ratios of Accretropin™ and Humatrope® for hGH AUCt, AUCinf, and Cmax were 94.23%, 96.88%, and 103.84%, respectively. The corresponding 90% confidence intervals were 88.70-100.10% for AUCt, 93.28-100.61% for AUCinf and 95.73-112.63% for Cmax.

In addition, the biologic and metabolic effects of hGH on IGF-1, IGFBP-3, and glucose were similar following administration of either Accretropin™ or Humatrope® (**Table 3**).

Table 3. Summary of IGF-1, IGFBP-3, and Glucose Levels after a Single Dose Administration of Accretropin™ or Humatrope®

Parameter	Treatment	Serum concentration at baseline, CV [%]	Serum concentration after 24 hours, CV [%]	AUC_{0-24}, CV [%]	AUC_{0-24} Ratio*, CV [%]
IGF-1	[redacted]	151.2 µg/L [29.3]	394.3 µg/L [20.0]	6133.56 µg·h/L [18.5]	98.94 (13.92)
	Humatrope®	151.4 µg/L [31.8]	412.9 µg/L [20.0]	6273.99 µg·h/L [20.43]	
IGFBP-3	[redacted]	2848.6 µg/L [23.6]	3385.0 µg/L [23.2]	70720.45 µg·h/L [20.43]	97.14 (15.38)
	Humatrope®	2997.5 µg/L [23.4]	3445.7 µg/L [21.3]	73234.85 µg·h/L [19.76]	
Glucose	[redacted]	5.5 mmol/L [8.1]	4.8 mmol/L [10.7]	140.45 mmol·h/L [8.54]	101.47 (5.94)
	Humatrope®	5.4 mmol/L [9.3]	4.8 mmol/L [10.6]	138.68 mmol·h/L [8.84]	

*[redacted]/Humatrope®

The sponsor stated that based on natural log-transformed hGH data, the 90% confidence intervals of ratios of the test and reference products for AUCs and Cmax are within the 80-125% requirements for bioequivalence. It was further concluded that the test product, Cangene's Accretropin™ is bioequivalent to the reference product, Eli Lilly's Humatrope®.

2.3 Analytical Section

1. How is hGH measured in serum in the clinical pharmacology study?

The sponsor stated that serum levels of hGH were measured by a validated enzyme linked immunosorbent assay (ELISA). A set of five non-zero standards ranging from 0.1875 ng/mL to 3.0 ng/mL were used. It was claimed that the validation showed that accuracy and precision met acceptable levels across the range of the method and so only one quality control level, known as the Internal Control Standard (ICS) was assayed on each plate. Repeat testing was performed on samples for which initial tests failed valid assay criteria such as poor replicate coefficient of variation (CV%), standard curve not meeting acceptance criteria, or other causes such as procedural errors. Eleven of the 48 sample sets required repeat testing of either all or part of the test. The result from the repeat experiment was used as the reportable value.

The validation report showed that the assay is accurate with percent recovery of 87 to 106% over the concentration range of 2 to 100 ng/mL. The assay is also precise with inter-assay precision of less than 16% for all concentrations tested including 2, 5, 10, 20, 50, and 100 ng/mL. The assay was specific with average recovery of 88%. The limit of quantitation was 0.1875 ng/mL. The sponsor provided an amendment for method validation where three QC standards were included in the hGH clinical ELISA in place of the ICS. The nominal concentrations of these QC standards are 0.22, 0.76, and 1.9 ng/mL. The results demonstrated that the inter-assay precision (%CV) was less than 9.55% for all QC standards.

The in-study validation data showed that between-run precision of ICS [redacted] for Study GA-002 was 7.30%. The concentrations for standard curve included 0.1875, 0.3750, 0.7500, 1.500, 3.0000 ng/mL. For all standard curve concentrations, between-run accuracy ranged from -6.14 to 5.01% of nominal values and between-run precision (%CV) ranged from 3.35% to 7.98%. Due to the supportive role of Study GA-002, the QC data provided by the sponsor are adequate.

3 Detailed Labeling Recommendations

[redacted]

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4 Appendix

4.1 Study Synopsis

[redacted] Human Growth Hormone Study
[redacted] Study No. 226-99-280 (GA-002 version 2.1) January 2002

2.0 SYNOPSIS

Name of Sponsor/Company: Cangene Corporation 104 Chancellor Matheson Road Winnipeg, Manitoba R3T 5Y3, Canada	Volume:	*(For National Authority Use only)*
Name of Finished Product: [redacted]	Page:	
Name of Active Ingredient: Recombinant Human Growth Hormone (rhGH)		
Title of Study: Comparative Bioavailabilty of [redacted] and Humatrope® in Somatostatin Suppressed Normal Subjects.		
Investigators: [redacted]		
Study Centre(s): Clinical Facility: [redacted] Statistical and Report Writing Facility: [redacted] Analytical Facilities: Cangene Corporation, Biotechnology Division, 26 Henlow Bay, Winnipeg, Manitoba R3Y 1G4, Canada [redacted]		
Study Period: (Dosing Date – Exit Date) Period 1: November 3, 1999 - November 4, 1999 Period 2: November 10, 1999 - November 11, 1999	*Phase of Development:* Phase I Study	
Objective: To compare the bioavailability of [redacted] to Humatrope® in Somatostatin suppressed normal, Healthy, non-smoking male subjects.		

2.0 SYNOPSIS *(Cont'd)*

Name of Sponsor/Company: Cangene Corporation 104 Chancellor Matheson Road Winnipeg, Manitoba R3T 5Y3, Canada	Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: [redacted]		
Name of Active Ingredient: Recombinant Human Growth Hormone (rhGH)		

Methodology:

- A single-dose, double-blind, standard randomized, two-way crossover study designed to compare the bioavailability of [redacted] and Humatrope® administered subcutaneously to Somatostatin suppressed, healthy, normal, non-smoking subjects, under fed condition.
- A total of 23 subjects received 4 mg of either [redacted] or Humatrope®.
- Safety and pharmacokinetic data as assessed by serum levels of human growth hormone (hGH) of all subjects who completed the study were determined.
- Pharmacodynamic parameters were assessed.

Number of subjects (planned and analyzed):

Twenty-four subjects were enrolled in the study.

Twenty-three subjects were dosed with either [redacted] or Humatrope® and twenty of these subjects completed the study. Serum samples from all 23 subjects dosed were analyzed for hGH, IGF-1, IGFBP-3 and glucose.

Diagnosis and main criteria for inclusion:

- Male.
- Age 18-55 years.
- Weight within the range 135-220 pounds (61-100 kg) and within ±15 % of normal for height and
- body frame as per the standard tables provided in Appendix III of the study protocol.
- Non-smoker.
- Basal endogenous hGH serum level below 5 ng/mL.
- Normal and healthy as determined by medical history, physical examination, electrocardiogram
- (ECG) and vital signs.
- Healthy as determined by results from tests of liver, kidney, and hematological functions.
- Granting written Informed Consent.
- Acceptable alcohol and drug screen at check-in.
- Testing negative for Anti-HIV (Human Immunodeficiency Virus),
- Anti-HBV (Hepatitis-B Virus) and Anti-HCV (Hepatitis-C Virus).

2.0 SYNOPSIS *(Cont'd)*

Name of Sponsor/Company: Cangene Corporation 104 Chancellor Matheson Road Winnipeg, Manitoba R3T 5Y3, Canada	Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: [redacted]		
Name of Active Ingredient: Recombinant Human Growth Hormone (rhGH)		

Test product: [redacted] (Cangene Corporation, Canada)
Batch (Lot) number: 4412803Z
Dose: 4 mg/subject
Mode of administration: Subcutaneous Injection

Reference product: Humatrope® (Eli Lilly and Company, Canada)
Batch (Lot) number: (L) 2MZ18R
Dose: 4 mg/subject
Mode of administration: Subcutaneous Injection

Duration of treatment:

One dose of [redacted] or Humatrope® was administered on November 3, 1999 to each subject, then on November 10, 1999 one dose of the alternate treatment was administered to the same subjects according to the randomization scheme.

Criteria for Evaluation:

Pharmacokinetics:
- The 90% confidence interval of the relative mean AUC_T of the test to reference formulation within 80 % to 125 %.
- The relative mean measured C_{max} of the test to reference formulation between 80 % and 125 %.

Safety:
Safety was assessed based on the severity and causality of adverse events experienced by subjects who underwent drug administration.

2.0 SYNOPSIS *(Cont'd)*

Name of Sponsor/Company: Cangene Corporation 104 Chancellor Matheson Road Winnipeg, Manitoba R3T 5Y3, Canada	Volume:	*(For National Authority Use only)*
Name of Finished Product: [redacted]	Page:	
Name of Active Ingredient: Recombinant Human Growth Hormone (rhGH)		

Statistical Methods:

Descriptive statistics were calculated for pharmacokinetic parameters of both test and reference products.

Analysis of Variance (ANOVA) was also carried out on the natural log-transformed AUC_T, AUC_I, and C_{max} parameters and on the untransformed t_{max}, λ, and $t_{½}$ parameters.The reported results included:

a) Geometric means of AUC_T, AUC_I, and C_{max} for both the test and reference products;
b) Ratios of geometric means of the test and reference products for AUC_T, AUC_I, and C_{max};
c) 90% confidence intervals of the AUC_T, AUC_I, and C_{max} ratios.

2.0 SYNOPSIS *(Cont'd)*

SUMMARY-CONCLUSION

PHARMACOKINETIC RESULTS
(N=20)

(Uncorrected for Measured Drug Content)

Parameter	Test (A)	Reference (B)	Ratio of Geom. Means (%)	90% Geom. Confidence Interval (%)	Intra-Subject CV(%)
	Geometric Mean Arithmetic Mean (CV,%)				
AUC_T (ng·h/mL)	232.93 238.09 (18.53)	247.20 254.09 (18.20)	94.23	88.70 – 100.10	10.80
AUC_I (ng·h/mL)	249.63 255.31 (16.85)	257.67 263.49 (17.38)	96.88	93.28 – 100.61	6.76
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t_{max}* (hours)	3.50 (1.20)	4.00 (1.37)	-		
λ* (h^{-1})	0.2103 (27.90)	0.2076 (20.28)	-		
$t_{½}$* (hours)	3.63 (36.75)	3.46 (18.21)	-		

* t_{max} is expressed as median (STD), λ and $t_{½}$ are expressed as arithmetic mean (CV,%) only.

(Corrected for Measured Drug Content)

Parameter	Test (A)	Reference (B)	Ratio of Geometric Means (%)	90% Geom. Confidence Interval (%)
	Geometric Mean			
AUC_T (ng·h /mL)	234.23	243.12	96.35	90.81 – 102.23
AUC_I (ng·h /mL)	251.03	253.42	99.06	95.46 – 102.81
C_{max} (ng/mL)	28.34	26.69	106.17	98.05 – 114.97

SAFETY RESULTS:

There were no safety concerns related to vital signs and physical findings during the conduct of the study. The test product [redacted], Cangene Corporation, Canada) was found to be as similarly well tolerated as the reference product (Humatrope®, Eli Lilly and Company, Canada), under single-dose conditions.

CONCLUSION:

Based on the results of the pharmacokinetic comparisons between Cangene's test product, [redacted], and Eli Lilly and Company's reference product, Humatrope®, [redacted] was found to be bioequivalent to Humatrope®, under single-dose conditions.

4.2 Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		**Information**
NDA Number	21-538	**Brand Name**	Accretropin
OCP Division	OCP 2	**Generic Name**	Somatropin
Medical Division	HFD-510	**Drug Class**	Protein
OCPB Reviewer	Xiaoxiong (Jim) Wei	**Indication(s)**	Growth hormone deficiency
OCPB Team Leader	Hae-Young Ahn	**Dosage Form**	solution
		Dosing Regimen	0.03mg/kg/day
Date of Submission	05-10-2006	**Route of Administration**	SC
Estimated Due Date of OCPB Review		**Sponsor**	Cangene, Canada
PDUFA Due Date	03-10-2007	**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**	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	1	1		
Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable?	**Yes**	June 21, 2006, The sponsor submitted analytical assay validation for human PK study (GA-002) after requested.		
Comments sent to firm?	**No**			

Briefing in Content:

The sponsor is seeking marketing their growth hormone under 505 (b) (1).

The sponsor conducted only one human pharmacokinetic study, in which bioequivalence between Accretropin and Humatrope was demonstrated in healthy subjects with somatostatin suppression. However, the study was conducted in 1999 using an early formulation, in which there were [redacted] amounts of phenol compared to the commercial formulation. The sponsor did not submit analytical assay and validation reports in the original submission. The sponsor provided the assay validation after requested.

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/s/

Wei Qiu
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Xiao-xiong Wei
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