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RESEARCH**

*APPLICATION NUMBER:*

**21-884**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
REVIEW**

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NDA: 21-884	Submission Date: 01/04/2005, 01/12/2005, 08/19/2005
Brand Name	iPlex™
Generic Name	rhIGF-1/rhIGFBP-3
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 Metabolic and Endocrine Drug Products (HFD-510)
Sponsor	Insmmed, Inc.
Relevant IND(s)	50,140
Submission Type; Code	Original
Formulation; Strength(s)	Solution, 60mg/mL (0.5 mL per vial)
Dosing regimen	The dosage is adjusted for the individual patient. It should be administered via subcutaneous injection at a starting dose of 1.0 mg/kg once daily. Dose can titrated up to a maximum of 2.0 mg/kg daily.
Indication	— treatment of children — with growth failure due to severe growth hormone insensitivity syndrome

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## **1. EXECUTIVE SUMMARY**

### **1.1 RECOMMENDATIONS**

From the Clinical Pharmacology and Biopharmaceutics standpoint, the application is acceptable. This recommendation should be conveyed to the sponsor as appropriate.

#### **1.2 Phase IV**

None.

#### **1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings**

The rhIGF-1/rhIGFBP-3 complex is a binary protein complex of recombinant human insulin-like growth factor I (rhIGF-I) and recombinant human insulin-like growth factor-binding protein-3 (rhIGFBP-3) for subcutaneous injection with molecular weight of 36,381. The two proteins are combined in a 1:1 molar ratio for formation of the rhIGF-1/rhIGFBP-3 complex. The purified rhIGF-1/rhIGFBP-3 complex is prepared to a final concentration of 60 mg/mL. rhIGF-I is the bioactive component of the rhIGF-1/rhIGFBP-3 complex. The rhIGF-1/rhIGFBP-3 complex is indicated for the long-term treatment of children and adolescents with growth failure due to severe growth hormone insensitivity syndrome (hereditary or acquired) resulting in IGF-I deficiency.

Growth hormone insensitivity syndrome (GHIS) is very rare disease, about a total of 200 patients of worldwide. The sponsor conducted 2 small PK studies in patients and one bioequivalence study in healthy adult subjects. All pharmacokinetic parameters show great variations within-study and between-study.

Study SK-GHIS-33 was an open-label study involving five pediatric patients with GHIS. Four of the five patients participating in this study were receiving chronic therapy of 80 µg/kg rhIGF-I. On Day 1 of the study, patients received two subcutaneous injections of 80 µg/kg rhIGF-I approximately ten hours apart. Following a minimum of a 2-month washout period from injections of rhIGF-I, patients received rhIGF-1/rhIGFBP-3 as single subcutaneous injections at doses of 0.5 and 1.0 mg/kg/dose with a 3-day interval between the two doses. One of these four subjects also received a single dose of 2.0 mg/kg of rhIGF-1/rhIGFBP-3. The half-life for IGF-1 was determined from 21 – 27 hours depending on subcutaneous doses.

During the drug development, the sponsor had two manufacturing facilities. One with development scale (DDP) manufactured at Inmed's former facility in Santa Clara, CA, was used in the Clinical Trial Cohort #1 for 12 month study with 19 patients. The other with commercial scale (CDP #1) manufactured at Avecia, Billingham, UK, was used Clinical Trial Cohort #2 for 6 month with 10 patients. The sponsor conducted a pharmacokinetic sub-study (INSM-110-303) within Clinical Trial Cohort #2 to further characterize the pharmacokinetics of rhIGF-I and rhIGFBP-3 and to compare the pharmacokinetic profiles using both drug products manufactured from those two manufacturing facilities following two single doses of 1.0 mg/kg rhIGF-1/rhIGFBP-3

separated by approximately one week washout period in four GHIS subjects. However, this study was not designed for a formal bioequivalence analysis. Results showed that half-life for IGF-1 ranged from 5.1 to 10.7 hours. The difference in pharmacokinetics between Study SK-GHIS-33 and Study INSM-110-303 may be explained in part by their different serum ALS levels, growth-hormone dependent serum proteins which associate with IGF-1/IGFBP-3 complex to further prolong the circulation half-life of IGF-1.

Since the manufacturing facility in Avecia, England is no longer available, the sponsor has planned to manufacture their to-be-marketed drug product (CDP #2) at Insmed Therapeutic Proteins Facility in Boulder, CO. On August 19, 2005, the sponsor submitted their bioequivalence study report. In a single dose, cross-over study in healthy adult volunteers, the pharmacokinetic profiles were compared following a subcutaneous administration of 0.5 mg/kg rhIGF-I/rhIGFBP-3 manufactured at two different manufacturing facilities. The pharmacokinetic parameters were analyzed using both approaches: baseline corrected and baseline uncorrected. It is rational using baseline corrected PK parameters to do BE analysis since the baseline contributed about 50% of the total exposure. The baseline corrected BE analysis showed that AUC (0-last) met the BE criteria, but Cmax was off slightly. Only a single time point at predose was measured and used as baseline, which may not be reliable. Baseline uncorrected BE analysis demonstrated that both AUC (0-last) and Cmax met BE criteria. Overall, utilizing both baseline corrected and uncorrected BE analyses, it is concluded that the drug product from these two sites are comparable.

Two ELISA methods, immunoassays were used to measure serum IGF-1 and IGFBP-3, respectively.

## 2. QUESTION BASED REVIEW

### 1.2 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?

IGF-1/IGFBP-3 is a binary protein complex of recombinant human insulin-like growth factor I (rhIGF-I) and recombinant human insulin-like growth factor-binding protein-3 (rhIGFBP-3) for subcutaneous injection with molecular weight of 36,381. rhIGF-I consists of 70 amino acid residues [i] with a molecular weight of 7,649 and rhIGFBP-3 consists of 264 amino acid residues [ii] with a molecular weight of 28,732. The amino acid sequence of rhIGF-I and rhIGFBP-3 are provided in Table 1.

**Table 1. Amino Acid Sequence of rhIGF-I and rhIGFBP-3**

Protein Subunit	Amino Acid Sequence
rhIGF-I	GPETLCGAELVDALQFVCGDRGFYFNKPTGYGSSRRAPO TGWDECCFRSCDLRRLEMYCAPLKPAKSA
rhIGFBP-3	GASSAGLGPVVRCEPCDARALAQCAPPAVCAELVREPGC GCCLTCALSEGQPCGIYTERCGSGLRCQSPDEARPLQALL DGRGLCVNASAVSRLRAYLLPAPPAPGNAESEEDRSAGS VESPSVSSTHRVSDPKFHPLHSHKIIKKGHAKDSORYKVDYE SQSTDTQNFSSSESKRETEYGPCRREMEDTLNHLKFLNVLSP RGVVFJIPNCDKKGFKYKKKOCRPSKGRKRGFCWCVDKYGQP LPGYTTKGKEDVHCYSMQSK

rhIGF-I/rhIGFBP-3 is produced by two separate *E. coli* strains: one containing the human gene for insulin-like growth factor I (IGF-I), the other containing the human gene for insulin-like growth factor-binding protein-3 (IGFBP-3). The two proteins are combined in a 1:1 molar ratio for formation of the rhIGF-I/rhIGFBP-3 complex. IGFBP-3 from human plasma is glycosylated, whereas rhIGFBP-3 produced in *E. coli* is non-glycosylated. Glycosylated and non-glycosylated IGFBP-3 bind IGF-I with similar affinities.

The purified rhIGF-I/rhIGFBP-3 complex is prepared to a final concentration of 60 mg/mL in 50 mM sodium acetate and 105 mM sodium chloride with a final pH of 5.5. rhIGF-I/rhIGFBP-3 for injection is a sterile, clear, colorless, to slightly yellow liquid available in a concentration of 60 mg/mL with a delivery volume of 0.5 mL. The composition of drug formulation is presented in Table 2.

**Table 2. Composition of the Drug Product Unit Dosage Form**

Component	Reference to Quality Standard	Function	Target Concentration	Quantity per Vial
rhIGF-I/ rhIGFBP-3	In-house standard	Active Ingredient	60 mg/mL	36mg
Sodium acetate	USP	~	50mM	/
Sodium chloride	USP	-	105mM	/

## 2.1.2 What is the mechanism of action, therapeutic indication and dosage recommendations for rhIGF-I/rhIGFBP-3?

### Mechanism of Action

rhIGF-I is the bioactive component of the rhIGF-I/rhIGFBP-3 complex. The primary pharmacologic effect of IGF-I in children is the promotion of linear growth. Secondary pharmacologic actions of IGF-I include the induction of insulin sensitization and insulin-like effects. In normal human circulation, less than 2% of total IGF-I exists in the free form. Most circulating IGF-I is found in association with the growth hormone (GH)-dependent IGFBP-3 and this binary complex further associates with a third serum protein, the GH-dependent acid-labile subunit (ALS), to form a ternary complex of ~150 kD. The ternary complex, consisting of one mole each of IGF-I, IGFBP-3 and ALS, is non-covalent in nature.

Unlike free IGF-I, which can readily cross the vascular endothelium, the ternary complex restricts IGF-I to the circulation due to its size, and increases IGF-I half-life from <15 min to > 12 hr. A small amount of free IGF-I is present in serum in equilibrium with the bound forms. In addition, proteolytic cleavage of IGFBP-3 and interaction of the ternary complex with proteoglycans have been shown to release IGF-I from the ternary complex.

### Proposed Indications

rhIGF-I/rhIGFBP-3 complex is indicated for the treatment of children with growth failure due to severe growth hormone insensitivity syndrome (hereditary or acquired) resulting in IGF-I deficiency and presenting with height standard deviation score less than or equal to -3 and IGF-I SDS less than or equal to -3.

### Proposed Dosage Recommendation

rhIGF-I/rhIGFBP-3 complex dosage and administration should be individualized for each patient. rhIGF-I/rhIGFBP-3 complex should be administered via subcutaneous injection at a starting dose of 1.0 mg/kg, given once daily. Dose can be titrated up to a maximum of 2.0 mg/kg daily. Dose should be adjusted downward in the event of adverse effects and/or IGF-I levels that are greater than or equal to 3 standard deviations above the normal reference range for IGF-I.

### 1.3 GENERAL CLINICAL PHARMACOLOGY

#### 2.2.1 What are the pharmacokinetic profiles of IGF1/IGFBP3 following a single subcutaneous administration in pediatric patients with Growth Hormone Insensitivity Syndrome (GHIS)?

Study SK-GHIS-33 was an open-label study involving five patients with GHIS. Four of the five subjects participating in this study were receiving chronic rhIGF-I therapy. Patients were instructed to continue therapy with rhIGF-I until the day before entering the study. On Day 1 of the study, subjects received two subcutaneous injections of 80 µg/kg rhIGF-I approximately ten hours apart. Following a minimum of a 2-month washout period from injections of rhIGF-I, subjects received rhIGF-I/rhIGFBP-3 as single subcutaneous injections at doses of 0.5 and 1.0 mg/kg/dose with a 3-day interval between the two doses. One of these four subjects also received a single dose of 2.0 mg/kg of rhIGF-I/rhIGFBP-3.

A fifth subject who had never been treated with rhIGF-I was also enrolled into the study. This subject received single subcutaneous injections of rhIGF-I/rhIGFBP-3 at doses of 1.0 and 2.0 mg/kg with a 7-day interval between the two doses.

For the first four subjects enrolled, serum samples for measurement of IGF-I and IGFBP-3 were collected just prior to administering rhIGF-I 80 µg/kg bid, and then 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 24 hours following the first injection. Approximately three months later, serum samples for measurement of IGF-I and IGFBP-3 were collected just prior to administering rhIGF-I/rhIGFBP-3 at 0.5 mg/kg, and then 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 24, 48 and 72 hours following the injection. The 72-hour sample was collected just prior to administering rhIGF-I/rhIGFBP-3 at 1.0 mg/kg and served as the baseline (0 hour) measurement for that treatment, with additional samples collected 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 24 hours following the injection. A fifth subject (Subject #5), who had never been treated previously with rhIGF-I, received a single dose of 1.0 mg/kg rhIGF-I/rhIGFBP-3. Serum samples were collected just prior to this injection and 6, 12, 18, 24, 36, 48, 60 and 72 hours following the injection. One week later this subject received a single dose of 2.0 mg/kg rhIGF-I/rhIGFBP-3. Serum samples were collected just prior to this injection and 6, 12, 18, 24, 36, 48, 60 and 72 hours following the injection. The pharmacokinetic parameters are summarized in Tables 3 and 4 and the time-concentrations profiles are presented in Figure 1.

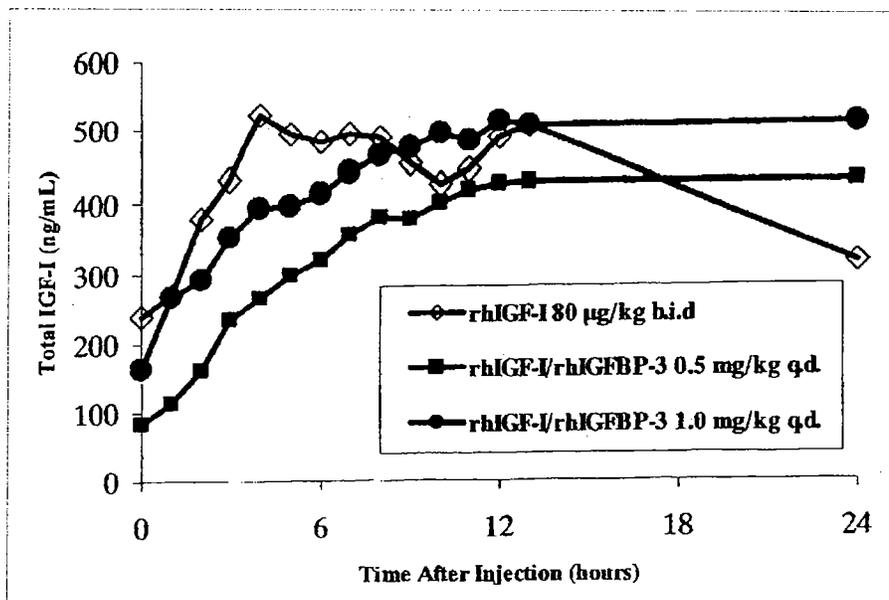
**Table 3. Summary of pharmacokinetic parameters for IGF-1 (baseline corrected)**

PK parameters	IGF-1	rhIGF/rhIGFBP3		
	Dose level			
	80 µg/kg BID	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg
Daily dose	160 µg/kg	105.1 µg/ml	210.2 µg/ml	420.5 µg/kg
Pre-dose Conc. (ng/mL)	163 (114) (N=4)	0.0 (0.0) (N=4)	63 (66) (N=5)	3.1 (4.4) (N=2)
C <sub>max</sub> (ng/mL)	451 (112) (N=4)	374 (119) (N=4)	459 (131) (N=5)	352 (-) (N=2)
T <sub>max</sub> (h)	8.0 (5.8) (N=4)	19 (8.3) (N=4)	17 (7) (N=5)	21 (-) (N=2)
AUC 0-24 (ng*hr/mL)	8155 (2191) (N=4)	6645 (2278) (N=4)	8184 (2501) (N=5)	6610 (-) (N=2)
AUC 0-last (ng*hr/mL)	8155(2191) (N=4)	16630 (7570) (N=4)	10208 (3672) (N=5)	17958 (-) (N=2)
AUC 0-∞ (ng*hr/mL)	8155 (2191) (N=4)	19275 (9894) (N=4)	19076 (-) (N=2)	22912 (-) (N=2)
Half-Life (h)	-	21.1 (4.2) (N=4)	24.5 (-) (N=1)	26.9 (-) (N=2)
V <sub>z</sub> /F (L/kg)	-	0.210 (0.13) (N=4)	0.389 (-) (N=1)	0.708 (-) (N=2)
Cl/F (L/h/kg)	0.0206 (0.0048) (N=4)	0.0074 (0.0055) (N=4)	0.0110 (-) (N=1)	0.0186 (-) (N=2)

**Table 4. Summary of pharmacokinetic parameters for IGFBP-3 (baseline corrected)**

PK parameters	IGF-1	rhIGF/rhIGFBP3		
	Dose level			
	80 µg/kg BID	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg
Daily dose	0 µg/kg	394.9 µg/ml	789.8 µg/ml	1579.5 µg/kg
Baseline (ng/mL)	1300 (630) (N=4)	1300 (580) (N=4)	1080 (550) (N=5)	2150 (-) (N=2)
C <sub>max</sub> (ng/mL)	480 (350) (N=4)	580 (260) (N=4)	770 (330) (N=5)	710 (-) (N=2)
T <sub>max</sub> (h)	3.8 (1.5) (N=4)	5.5 (1.7) (N=4)	9.4 (8.3) (N=5)	15 (-) (N=2)
AUC 0-24 (ng*hr/mL)	2260 (1980) (N=4)	6210 (5040) (N=4)	10330 (6330) (N=5)	79800 (-) (N=2)
AUC 0-last (ng*hr/mL)	2260 (1980) (N=4)	12860 (12810) (N=4)	15130 (7510) (N=5)	16530 (-) (N=2)

**Figure 1. Mean total serum IGF-I levels following subcutaneous injections of 80 ug/kg rhIGF-I BID 0.5 mg/kg rhIGF-I/rhIGFBP-3 and 1.0 mg/kg rhIGF-I/rhIGFBP-3**



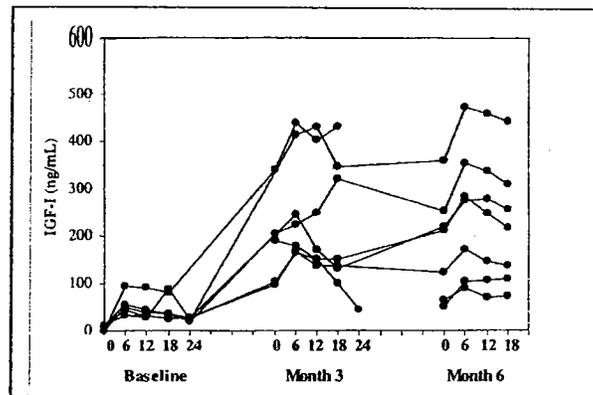
**Reviewer's comments:**

One of study objectives was to compare the relative exposure of regular IGF-1 80µg/kg dose of regular IGF-1 to 0.5–2.0 mg/kg of IGF-1/IGFBP-3. The exposure from 80 µg/kg of regular IGF-1 is actually within the range of exposure from 0.5 mg/kg to 2.0 mg/kg of IGF-1/IGFBP-3 complex. However, pre-determined 3 day interval between the doses of 0.5 mg/kg and 1.0 mg/kg apparently was not long enough to let baseline return to predose levels. Sampling points were not frequent enough to reliably determine t1/2. Substantial accumulation at predose, baseline corrected PK may be misleading and not reliable.

**2.2.2 What are the steady state pharmacokinetic profiles of IGF-1/IGFBP-3 in pediatric patients with Growth Hormone Insensitivity Syndrome (GHIS)?**

In Study INSM-110-303 Cohort #1 (total 19 patients), serum samples were collected prior to and 6, 12, 18, and 24 hours after the first dose (0.5 mg/kg) on Day 1 and prior to and 6, 12, 18 hours after dosing (1.0 mg/kg) at Months 3, and 6 for measurement of IGF-1, IGFBP-3. Five, five and eight patients participated in baseline, Month 3 and Month 6 pharmacokinetic monitoring, respectively. Results of IGF-1 serum concentrations at baseline and Month 3 and Month 6 are shown in Figure 2.

**Figure 2. Steady state IGF-1 concentrations in the 24-hour surveillance population (baseline uncorrected).**



These data indicates that the steady state serum concentrations of IGF-1 at Month 3 and Month 6 were similar.

## 2.3 GENERAL BIOPHARMACEUTICS

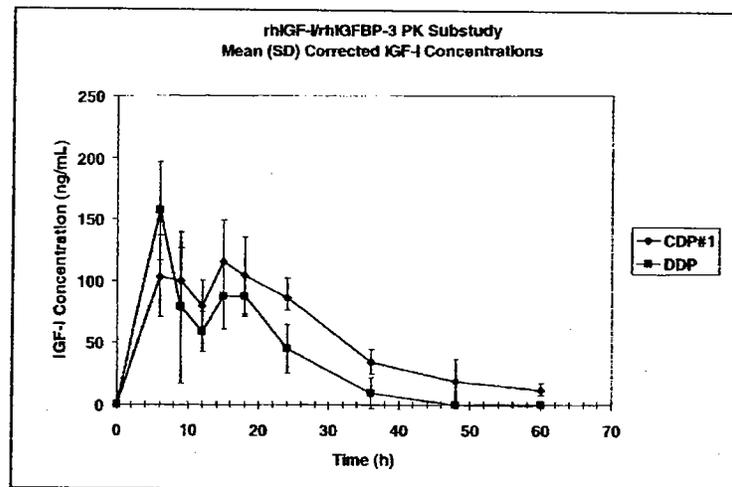
### 2.3.1 Is the IGF-1/IGFBP-3 drug products manufactured in Santa Clara, California in development scale (DDP) comparable to the drug products manufactured at Avecia, Billingham, UK in commercial scale (CDP#1)?

During drug development the sponsor had two manufacturing sites: one for the Development Drug Product (DDP) with development scale manufactured at Insmad's former facility in Santa Clara, CA, was used in the Clinical Trial Cohort #1 for 12 month study with 19 patients; the other for the Commercial Drug Product #1 (CDP #1) with commercial scale manufactured at Avecia, Billingham, UK, was used Clinical Trial Cohort #2 for 6 month with 10 patients. The sponsor conducted a pharmacokinetic sub-study within Clinical Trial Cohort #2 to further characterize the pharmacokinetics of rhIGF-I and rhIGFBP-3 and to compare the pharmacokinetic profiles for drug products manufactured at two different manufacturing facilities following two single doses of 1.0 mg/kg rhIGF-/rhIGFBP-3 separated by approximately one week washout period in four GHIS subjects. This study was not designed for a formal bioequivalence study. The results are summarized in Table 4 and Figures 3 and 4.

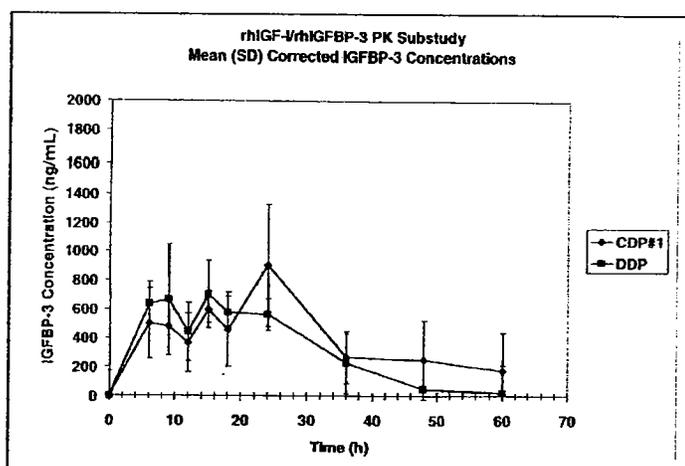
**Table 4. Summary of pharmacokinetic parameters of IGF-1 and IGFBP-3 following a single dose of 1 mg/kg (baseline corrected) (Mean  $\pm$ SD, N=4)**

PK parameters	IGF-1		IGFBP3	
	DDP	CDP#1	DDP	CDP#1
<b>C<sub>max</sub></b> (ng/mL)	157 (40) (N=4)	127 (25) (N=4)	857 (184) (N=4)	920 (603) (N=4)
<b>T<sub>max</sub></b> (h)	6.0 (0.0) (N=4)	11.3 (6.2) (N=4)	12.0 (5.5) (N=4)	19.5 (9.0) (N=4)
<b>AUC 0-24</b> (ng*hr/mL)	1908 (552) (N=4)	2073 (464) (N=4)	12585 (3564) (N=4)	11344 (5871) (N=4)
<b>AUC 0-60</b> (ng*hr/mL)	2202 (726) (N=4)	3299 (643) (N=4)	19282 (3560) (N=4)	23834 (13149) (N=2)
<b>AUC 0-<math>\infty</math></b> (ng*hr/mL)	2337 (859) (N=4)	3506 (794) (N=4)	20586 (2307) (N=2)	37416 (2181) (N=2)
<b>Half-Life</b> (h)	5.1 (3.0) N=4	10.7 (5.4) (N=4)	9.9 (4.0) (N=2)	9.0 (2.2) (N=2)
<b>V<sub>z</sub>/F</b> (L/kg)	634 (145) N=4	885 (349) (N=4)	560 (257) (N=4)	278 (84) (N=2)
<b>CL/F</b> (L/h/kg)	98.46 (31.79) (N=4)	62.40 (14.43) (N=4)	38.73 (4.35) (N=4)	21.14 (1.23) (N=2)

**Figure 3. Mean (SD) Serum IGF-I Concentration-Time Profiles (baseline corrected).**



**Figure 4. Mean (SD) Actual Serum IGFBP-3 Concentration-Time Profiles (baseline corrected).**



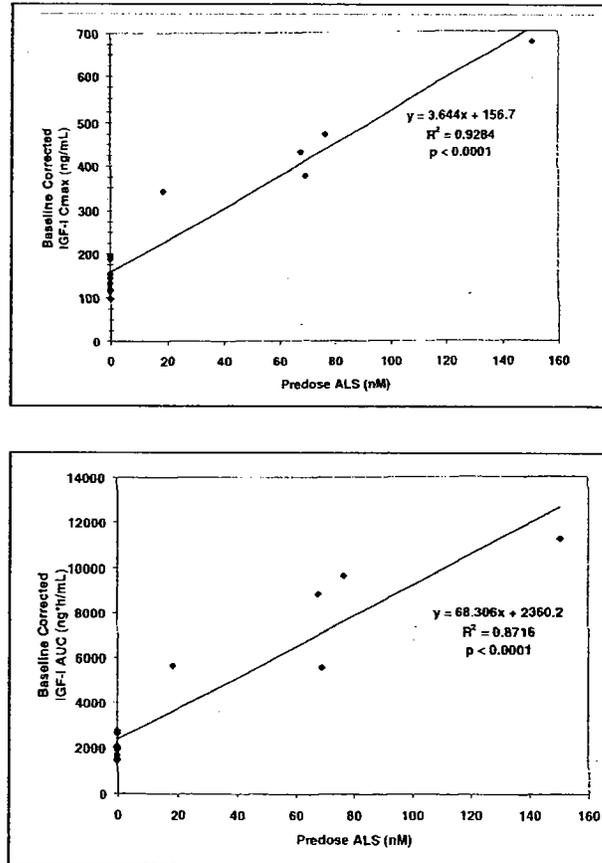
**Reviewer's comments:**

DDP was used in clinical trial Cohort 1 with 19 patients. CDP#1 was used in clinical trial Cohort #2 with 10 patients and a sub study with 4 patients for pharmacokinetics. From PK comparison, CDP#1 drug products exhibited about 50% more in AUC(0-last) and doubled the t1/2 from 5.1 hours to 10.7 hours. These two drug products are not comparable based on their pharmacokinetic performance. Since CDP#1 drug products were used Clinical trial Cohort #2 with 10 patients, the comparability between these two drug products in clinical efficacy and safety will be judged by the medical reviewer.

**2.3.2 Why are they so much different in the pharmacokinetic parameters of IGF-1 between Study SK-GHIS-33 and Study INSM-PK-303?**

By comparing Study SK-GHIS-33 with Study INSM-110-303, IGF-1 concentrations in Study SK-GHIS-33 were 3-4 fold those in Study INSM-110-303. However, IGFBP-3 levels exhibited little difference between these two studies since the exposure was only 21% to 27% higher in Study 303 than that in Study 33. To explain the difference in IGF-1 levels, the sponsor pointed out that the patients in Study 33 were not as severely sick as patients in Study 303. Patients in Study 33 had measurable ALS levels, which prolonged the circulation half-life of IGF-1. On the contrary, patients in Study 303 were severely ill with GHIS and they did not have detectable ALS levels in serum. The sponsor conducted a analysis of correlation between serum IGF-1 levels and serum ALS levels (Figure 5).

**Figure 5. Pre-dose ALS vs. Cmax and AUC(0-24) using 1.0 mg/kg data from GHIS-33 and PK Sub-study (INSM-110-303). The top and bottom panels provides the relationship between baseline corrected Cmax and AUC(0-24 hrs), respectively.**



Therefore, the difference between these two studies may be partially explained by their different ALS levels in patients.

**2.3.3 Are the IGF-1/IGFBP-3 drug products manufactured at Avecia, Billingham, UK in development scale (DDP) bioequivalent to the drug products manufactured at Boulder, Colorado (CDP#2)?**

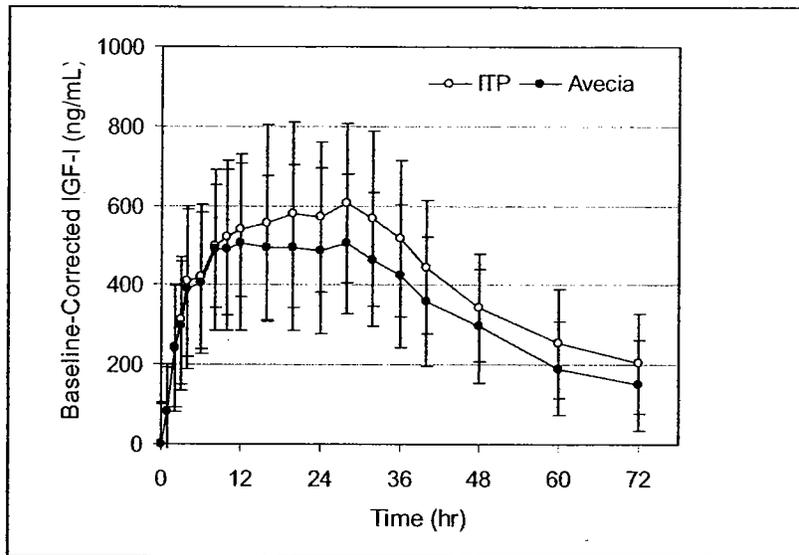
Since the manufacturing facility in Avecia, England is no longer available, the sponsor has planned to manufacture their Commercial Drug Product #2 (CDP #2) with commercial scale at Insmmed Therapeutic Proteins in Boulder, CO. Following a meeting with the Agency in July 12, 2005, the sponsor has submitted a protocol dated July 22, 2005 to the Agency for a phase 1 study in healthy adult volunteers to compare the pharmacokinetic profiles between their drug products manufactured at Avecia Facility (CDP#1, reference drug products) and Boulder Facility (CDP#2, test drug products). On August 19, 2005, the sponsor submitted their bioequivalence study report.

The sponsor conducted a Phase I, single dose, randomized, cross-over study in healthy, adult volunteers to compare the pharmacokinetic profiles of subcutaneous administration of 0.5 mg/kg rhIGF-I/rhIGFBP-3 manufactured at two different manufacturing facilities. Avecia drug product was used as the reference drug product to compare with Insmed Therapeutic Proteins drug product. The pharmacokinetic parameters were analyzed using both approaches: baseline corrected and baseline uncorrected. A single predose IGF-1 measurement was used as the baseline. The results are presented in Table 5 and Figures 6 and 7.

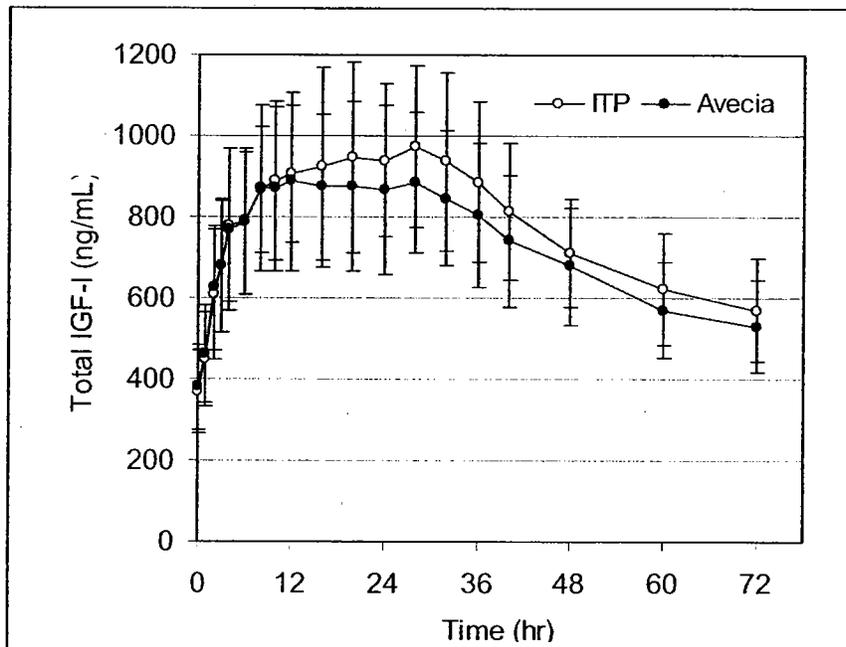
**Table 5. IGF-I pharmacokinetic parameters for bioequivalence after administration of a single dose of Avecia drug product and ITP drug product (N=28)**

IGF-I PK Parameters	Baseline Corrected		Uncorrected	
	Avecia Drug	ITP Drug	Avecia Drug	ITP Drug
<b>AUC<sub>0-last</sub> (ng/ml*hr)</b>				
Mean ± SD	25262 ± 6514.7	29684 ± 6850.4	52682 ± 10066.1	56184 ± 10350.2
Geometric Mean	24493	28908	51593	55134
ITP /Avecia Ratio (90% CI)	1.18 (1.11 – 1.25)		1.07 1.04 – 1.09	
<b>AUC<sub>0-∞</sub> (ng/ml*hr)</b>				
Mean ± SD	31536 ± 8083.4	38049 ± 8951.0	103606 ± 43461.4	105875 ± 31764.9
Geometric Mean	30480	36950	97851	101733
ITP /Avecia Ratio (90% CI)	1.21 (1.11 – 1.33)		1.04 (0.98 – 1.10)	
<b>C<sub>max</sub> (ng/ml)</b>				
Mean ± SD	594 ± 172.8	721 ± 209.5	974 ± 206.3	1089 ± 251.1
Geometric Mean	573	698	951	1065
ITP /Avecia Ratio (90% CI)	1.22 1.13 – 1.31		1.12 1.06 – 1.18	

**Figure 6. Comparison of mean ( $\pm$  SD) baseline-corrected IGF-I serum concentrations after administration of Avecia and ITP drug products**



**Figure 7. Comparison of mean ( $\pm$  SD) uncorrected IGF-I serum concentrations after administration of Avecia and ITP drug products**



**Reviewer's comments:**

This BE study was conducted in healthy subjects, who had normal endogenous IGF-1 levels comprising of about 50% of the total exposure and early exposure. With such substantial contribution of baseline in IGF-1, it is rational using baseline corrected PK parameters to do BE analysis. However, only a single time point at predose was measured for endogenous IGF-1 levels, which may not truly represent the physiological dynamics of endogenous IGF-1. We have little knowledge about the dynamics of endogenous IGF-1. The baseline corrected BE analysis seems to be more sensitive for comparability testing, but a single predose baseline correction may not be reliable. Furthermore, though it shows slightly off the upper limit of 90% confidence interval (1.31) for Cmax that is usually more variable, AUC(0-last) remains within 90% CI using baseline corrected BE analysis. Using baseline uncorrected analysis, both Cmax and AUC(0-last) pass the 90% CI. Overall, based on both baseline corrected and uncorrected analyses, we determine the two drug products are comparable in terms of PK perspective. Therefore, the sponsor has established comparability between new drug products produced in Boulder CO and the reference drug products used in Cohort #2.

**2.3.3 What is the relationship between clinical trials and formulations?**

During drug development, the sponsor had developed a few different formulations with different scales. The early drug formulations were in lower concentrations as 10 mg/mL and used three early stage exploratory PK studies including IV dosing (Table 6).

**Table 6. Development of Drug Formulation**

Study No.	Description	Formulation (rhIGF-1/rhIGFBP-3 concentrations)
9601	Early stage Phase 1, safety and PK of single IV dose	10 mg/mL
9602	Early stage Phase 1, safety and PK of multiple IV dose	10 mg/mL
9604	Early stage Phase 1, safety PK and 7 days s.c. infusion	10 mg/mL
SK-GHIS-33	Phase I, dose escalation PK in GHIS	60 mg/mL
INSM-110-303	Phase II/III, 12 months GHIS, S.C. injection	60 mg/mL
INSM-110-601	Phase I, BE study in healthy subjects	60 mg/mL

**2.4. ANALYTICAL**

**2.4.1 Analysis of Serum IGF-1**

The serum concentrations of IGF-1, which is an immunoassay. In the assay,

ELISA was used to measure

A set of IGF-I standards is used to plot a standard curve of absorbance versus IGF-I concentrations from which the IGF-I concentrations in the unknowns can be calculated.

**Table 7. Assay validation results for serum IGF-1 samples**

Precision (%CV)	
Accuracy	
Linearity	ng/mL
Sensitivity	LOO: ng/mL
Specificity	

### 2.4.2 Analysis of serum IGFBP-3

The ELISA was used to measure serum IGFBP-3 concentrations, which is an immunoassay. In the assay,

A set of IGFBP-3 standards is used to plot a standard curve of absorbance versus IGFBP-3 concentration from which the IGFBP-3 concentrations in the unknowns can be calculated.

**Table 8. Assay validation results for serum IGFBP-3 samples**

Precision (%CV)	
Accuracy	
Linearity	
Sensitivity	LOQ: ng/mL
Specificity	

## 3. DETAILED LABELING RECOMMENDATIONS

**4. APPENDICES**

**4.1 PROPOSED LABELING**

Not attached

**4.2 INDIVIDUAL STUDY REVIEW**

See Addendum

**4.3 FILING MEMO**

Office of Clinical Pharmacology and Biopharmaceutics <i>New Drug Application Filing and Review Form</i>				
<i>General Information About the Submission</i>				
NDA Number	21-884	Brand Name	Mecasermin rinfabate	
OCPB Division (I, II, III)	DPE II	Generic Name	rhIGF-1/rhIGFBP-3	
Medical Division	HFD-510	Drug Class	Growth hormone	
OCPB Reviewer	Xiaoxiong (Jim) Wei	Indication(s)	Growth hormone insensitivity syndrome	
OCPB Team Leader	Hae-Young Ahn	Dosage Form	60 mg/mL	
		Dosing Regimen	1 – 2 mg/kg daily	
Date of Submission	12-31-04	Route of Administration	Subcutaneous injection	
Estimated Due Date of OCPB Review	05-20-05	Sponsor	Insmed, Inc.	
PDUFA Due Date	06-31-05	Priority Classification	P1	
Final Due Date	05-31-05			
<b>1 Clin. Pharm. and Biopharm. Information</b>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
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			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	1		
multiple dose:	X	2		

<b>Patients-</b>				
single dose:	X	2		
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		5		
<b>ability and QBR comments</b>				
	"X" if yes	Comments		
ation fileable?	YES			
ents sent to firm?	NO			

**Briefing in Content:**

The drug product is a binary protein complex of recombinant human insulin-like growth factor I (rhIGF-I) and recombinant human insulin-like growth factor-binding protein-3 (rhIGFBP-3) for subcutaneous injection and is indicated for the treatment of growth failure due to severe growth hormone insensitivity syndrome (hereditary or acquired) resulting in IGF-I deficiency and presenting with height standard deviation score less than or equal to -3 and IGF-I SDS less than or equal to

The sponsor submitted 5 PK studies including one single dose PK study in healthy subjects, one multiple dose PK study in healthy subjects, one continuous subcutaneous infusion PK in healthy subjects, two single dose studies in patients with GHIS.

- 
- iii. Boonen S, Rosen C, Bouillon R, Sommer A, McKay M, Rosen D, et al. Musculoskeletal effects of the recombinant human IGF-1/IGF binding protein-3 complex in osteoporotic patients with proximal femoral fracture: a double-blind, placebo-controlled pilot study. *J Clin Endocrinol Metab.* 2002;87:1593-1599.
  - iv.. Debroy MA, Wolf SE, Zhang XJ, Chinkes DL, Ferrando AA, Wolfe RR, et al. Anabolic effects of insulin-like growth factor in combination with insulin-like growth factor binding protein-3 in severely burned adults. *J Trauma.* 1999;47:904-911.
  - v. Clemmons DR, Moses AC, McKay MJ, Sommer A, Rosen DM, Ruckle J. The combination of insulin-like growth factor I and insulin-like growth factor-binding protein-3 reduces insulin requirements in insulin-dependent type 1 diabetes: evidence for in vivo biological activity. *J Clin Endocrinol Metab.* 2000;85:1518-1524.

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

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Xiao-xiong Wei  
9/14/2005 11:19:40 AM  
BIOPHARMACEUTICS

Hae-Young Ahn  
9/14/2005 04:14:30 PM  
BIOPHARMACEUTICS

## Addendum

### 4.2 Individual Study Review

**NDA:** 21-884 (N-000)

**Drug name:** rhIGF-1/rhIGFBP-3

**Indication:** — treatment of children — with growth failure due to severe growth hormone insensitivity syndrome

**Submission date:** 01/04/2005, 01/12/2005, 08/19/2005

**Reviewer:** Xiaoxiong (Jim) Wei

**Team Leader:** Hae-Young Ahn

**OCPB:** DPE2

**OND:** DMEDP (Division of Metabolic and Endocrine Drug Products, HFD-510)

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	<b>Study #</b>	<b>Title</b>	<b>Page</b>
1	<b>SK-GHIS-33</b>	Phase I clinical trial of rhIGF-1/rhIGFBP-3 and rhIGF-I in children and adolescents with growth hormone Sensitivity syndrome (GHIS)	2
2	<b>INSM-110-303</b>	Pharmacokinetic Sub-study for a Phase II/III, Open-Label, Multi-Center Clinical Trial to Evacuate the Safety and Efficacy of an Insulin-Like Growth Factor-1/ Insulin-Like Growth Factor Binding Protein-3 Complex (rhIGF-1/rhIGFBP-3), Administered for 12 Months (Followed by a 12-Month Extension) in Children and Adolescents with Growth Hormone Insensitivity Syndrome (GHIS) such as Laron Syndrome.	10
3	<b>9601</b>	A Phase I Study of the Safety and Pharmacokinetics of Single Intravenous Doses of Recombinant Human Insulin Like Growth Factor-1/Insulin Like Growth Factor Binding Protein-3 (rhIGF-1/IGFBP-3)	18
4	<b>9602</b>	A Phase I Study of the Safety and Pharmacokinetics of Multiple Intravenous Doses of Recombinant Human Insulin Like Growth Factor-1/Insulin Like Growth Factor Binding Protein-3 (rhJGF-1/IGFBP-3).	22
5	<b>9604</b>	A Phase I Study of the Safety and Pharmacokinetics of Continuous Subcutaneous Infusion of Recombinant Human Insulin Like Growth Factor-1/Insulin Like Growth Factor Binding Protein-3 (rhIGF-1/IGFBP-3) for Seven Days in Healthy Elderly Female Subjects.	27
6	<b>INSM-110-601</b>	A Phase I, Single Dose, Randomized, Cross-Over Study in Healthy, Adult Volunteers, Comparing the Safety, Tolerability and Pharmacokinetic Profiles of Subcutaneous Administration of recombinant human Insulin-Like Growth Factor-I / recombinant human Insulin-Like Growth Factor Binding Protein-3 (rhIGF-1/rhIGFBP-3) Manufactured at Two Different Manufacturing Facilities	30

**Protocol No.: SK-GHIS-33**

**Title:** Phase I clinical trial of rhIGF-I/rhIGFBP-3 and rhIGF-I in children and adolescents with growth hormone Sensitivity syndrome (GHIS)

**Study period:** April 2002 - December 2003

**Objectives:** To evaluate the safety, tolerability and pharmacokinetic profiles of IGF-I and IGFBP-3 following administration of rhIGF-I or rhIGF-1/rhIGFBP-3 to subjects with GHIS.

**Methodology:** Four (4) subjects were studied at the end of chronic 80 µg/kg rhIGF-1 bid treatment followed by a two-month washout period during which time they received no treatment. Following the washout period subjects received single subcutaneous injections of 0.5 and 1.0 mg/kg/dose of rhIGF-1 /rhIGFBP-3 with a Three-day interval between doses.

One (1) of these four subjects also received rhIGF-1/rhIGFBP-3 at a dose of 1.0 mg/kg/day for five consecutive days (starting 96 hours after the initial 1.0 mg/kg dose). This subject later received a single dose of 2.0 mg/kg rhIGF-I/rhIGFBP-3.

One (1) additional subject, who had never previously received rhIGF-1 treatment, received single subcutaneous injections of 1.0 and 2.0 mg/kg rhIGF-1/rhIGFBP-3 with a 7-day washout between injections.

**Number of Subjects:** Five (1 female and 4 males)

**Diagnosis and Main Criteria for Inclusion:** Subjects with confirmed diagnosis of GHIS of genetic Origin.

**Test Product, Dose, Mode of Administration, Batch Numbers:** rhIGF-1/rhIGFBP-3 at doses of 0.5, 1.0 and 2.0 mg/kg was administered by subcutaneous injection. rhIGF-1/rhIGFBP-3 drug product was supplied by Insmad Incorporated and came from Lot number DP0001.

**Reference Therapy, Dose and Mode of Administration:** rhIGF-1 at a dose of 80 µg/kg bid by subcutaneous injection. rhIGF-1 was supplied to the investigator by Pharmacia, Sweden..

**Duration of Treatment:**

3 subjects were treated for the following duration:

- 1 day (2 doses) 80 µg/kg/dose rhIGF-1
- 1 day (1 dose) 0.5 mg/kg/dose rhIGF-1/rhIGFBP-3
- 1 day (1 dose) 1.0 mg/kg/dose rhIGF-1/rhIGFBP -3

1 subject was treated for the following duration:

- 1 day (2 doses) 80 µg/kg/dose rhIGF-1
- 1 day (1 dose) 0.5 mg/kg/dose rhIGF-1/rhIGFBP -3
- 6 days (6 doses) 1.0 mg/kg/dose rhIGF-1/rhIGFBP-3
- 1 day (1 dose) 2.0 mg/kg/dose rhIGF-1/rhIGFBP -3

1 subject was treated for the following duration:

- 1 day (1 dose) 1.0 mg/kg/dose rhIGF-1/rhIGFBP-3

- 1 day (1 dose) 2.0 mg/kg/dose rhIGF-1/rhIGFBP-3

**Criteria for Evaluation:**

**Pharmacokinetic:** All subjects who completed the study as planned and have sufficient pharmacokinetic data are included in the pharmacokinetic analyses.

**Safety:** All subjects who received at least one dose of study treatment are included in the safety analyses.

**Statistical Methods:** Because of the small number of subjects in this study, comparisons between treatment groups are made using summary statistics and frequency counts only.

**Pharmacokinetic Results:** Baseline corrected pharmacokinetic parameters for chronic dosing of rhIGF-I and single dosing of rhIGF-I/rhIGFBP-3 are presented in the following table:

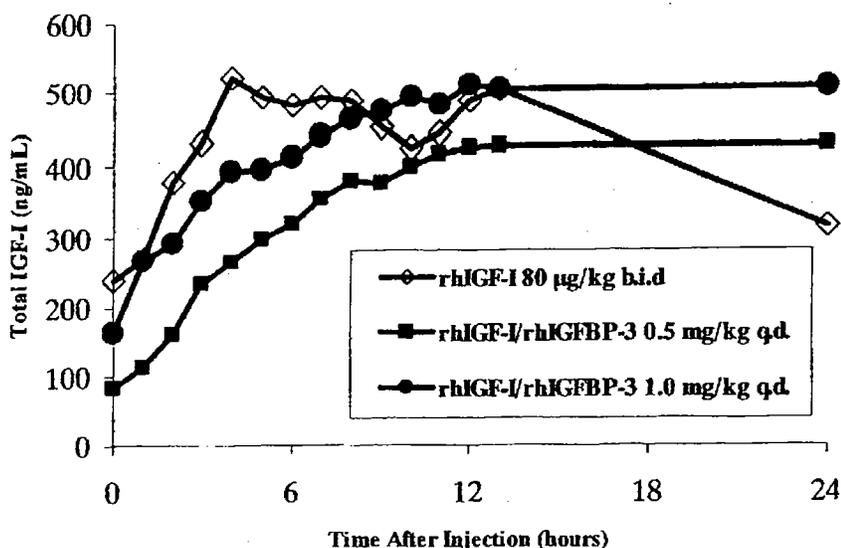
**Table 1a. Summary of pharmacokinetic parameters for IGF-I (uncorrected values)**

PK parameters	IGF-1	rhIGF/rhIGFBP3		
	80 ug/kg BID	Dose level		
Daily dose	160 ug/kg	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg
Predose Conc. (ng/mL)	239 (132) N=4	105.1 ug/ml 84.0 (32.6) (N=4)	210.2 ug/ml 142 (94) (N=5)	420.5 ug/kg 79 (15) (N=2)
C <sub>max</sub> (ng/mL)	535 (82) (N=4)	458 (150) (N=4)	539 (154) (N=5)	438 (-) (N=2)
T <sub>max</sub> (h)	8.0 (5.8) (N=4)	19 (8.3) (N=4)	16.8 (6.7) (N=5)	21 (-) (N=2)
AUC 0-last (ng*hr/mL)	10165 (1689) (N=4)	22678 (9820) (N=4)	16796 (9737) (N=5)	24120 (-) (N=2)
AUC 0-24 (ng*hr/mL)	10165 (1689) (N=4)	8661 (3040) (N=4)	10095 (3127) (N=4)	8634 (-) (N=2)
AUC 0-∞ (ng*hr/mL)	10165 (1689) (N=4)	30438 (14988) (N=4)	32172 (-) (N=2)	36689 (-) (N=2)
Half-Life (h)	-	30.5 (6.6) (N=4)	33.0 (-) (N=2)	40.9 (-) (N=2)
V <sub>z</sub> /F (L/kg)	-	0.184 (0.090) (N=4)	0.318 (-) (N=2)	0.678 (-) (N=2)
Cl/F (L/h/kg)	0.0161 (0.0028) (N=4)	0.0047 (0.0034) (N=4)	0.0067 (-) (N=2)	0.0115 (-) (N=2)

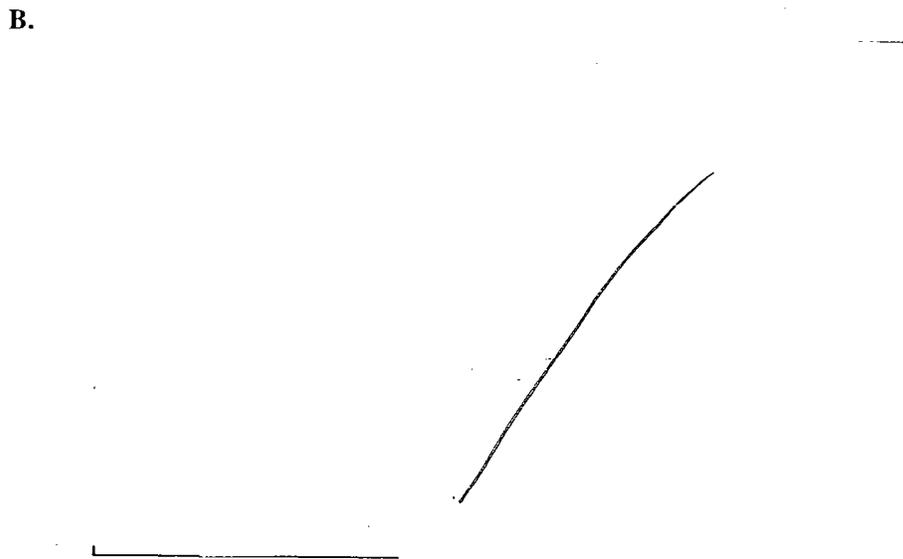
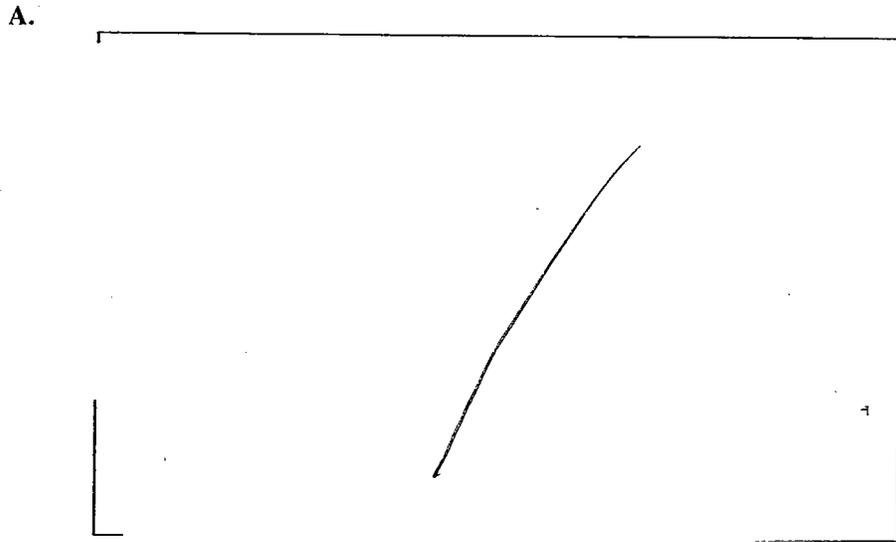
**Table 1b. Summary of pharmacokinetic parameters for IGF-I (corrected values)**  
**IGF-1** **rhIGF/rhIGFBP3**

PK parameters	Dose level			
	80 ug/kg BID	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg
Daily dose	160 ug/kg	105.1 ug/ml	210.2 ug/ml	420.5 ug/kg
Predose Conc. (ng/mL)	163(114) (N=4)	0 (0) (N=4)	63(66) (N=5)	3.1 (4.4) (N=2)
Cmax (ng/mL)	451 (112) (N=4)	374 (119) (N=4)	459 (131) (N=5)	352 (-) (N=2)
Tmax (h)	8.0 (5.8) (N=4)	19 (8.3) (N=4)	17 (7) (N=5)	21 (-) (N=2)
AUC 0-last (ng*hr/mL)	8155 (2191) (N=4)	16630 (7570) (N=4)	10208 (3672) (N=5)	17958 (-) (N=2)
AUC 0-24 (ng*hr/mL)	8155 (2191) (N=4)	6645 (2278) (N=4)	8184 (2501) (N=5)	6610 (-) (N=2)
AUC 0-∞ (ng*hr/mL)	8155 (2191) (N=4)	19275 (9894) (N=4)	19076 (-) (N=1)	22912 (-) (N=2)
Half-Life (h)	-	21.1 (4.2) (N=4)	24.5 (-) (N=1)	26.9 (-) (N=2)
Vz/F (L/kg)	-	0.210 (0.13) (N=4)	0.389 (-) (N=1)	0.708 (-) (N=2)
Cl/F (L/h/kg)	0.0206 (0.0048) (N=4)	0.0074 (0.0055) (N=4)	0.0110 (-) (N=1)	0.0186 (-) (N=2)

**Figure 1. Mean Total Serum IGF-I Levels Following Subcutaneous Injections of 80 ug/kg rhIGF-I b.i.d, 0.5 mg/kg rhIGF-I/rhIGFBP-3 and 1.0 mg/kg rhIGF-I/rhIGFBP-3**



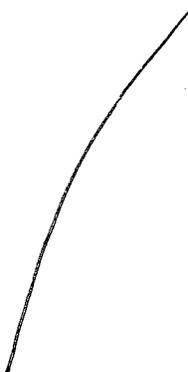
**Figure 2. Serum concentrations of IGFBP-3 obtained after chronic dosing of IGF-1 80 ug/kg bid (A), and after a single dose of 0.5 (B), 1.0 (C) and 2.0 (D) mg/kg rhIGF-I/rhIGFBP-3.**



C.

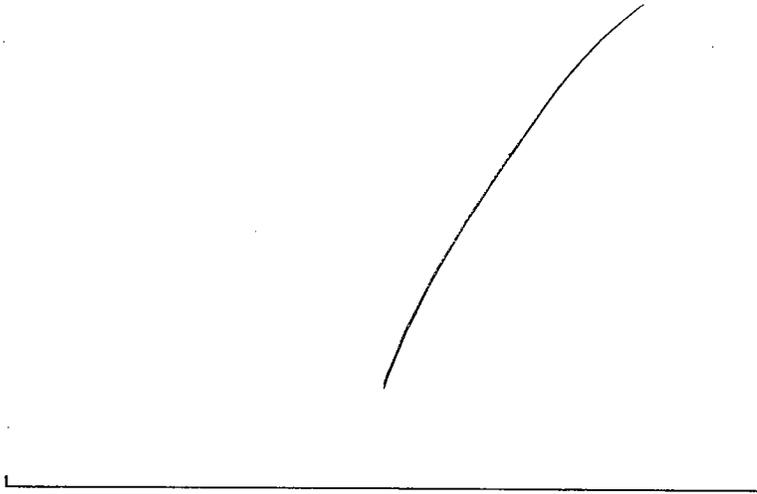


D.

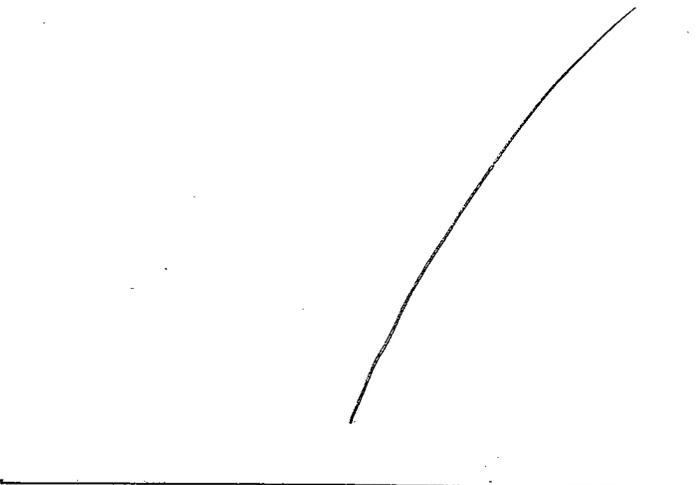


**Figure 3. Subject E2-15M IGF-I (A) and IGFBP-3 (B) Concentrations After Multiple Doses of 1.0 mg/kg/day rhIGF-I/rhIGFBP-3.**

**A.**



**B.**



All treatments produced mean  $C_{max}$  levels for serum total IGF-I within the normal range for age and sex.

The mean  $T_{max}$  value following administration of the first dose of rhIGF-I was 4.3 hours whereas the mean  $T_{max}$  values following administration of rhIGP-JJrhIGFBP-3 ranged between 17-21 hours, thus demonstrating slower absorption with rhIGF-I/rhIGFBP-3.

The mean uncorrected IGF-I  $AUC(0-\infty)$  value following 0.5 mg/kg rhIGF-I/rhIGFBP-3 qd (105 ug rhIGF-I equivalents) was approximately 3-fold greater than the mean  $AUC(0-\infty)$  value (where  $AUC(\tau) = AUC(0-\infty)$ ) following 80 ug/kg rhIGF-I bid (160 ug/day rhIGF-I equivalents). When

baseline-corrected data are assessed, administration of 0.5 mg/kg rhIGF-1/rhIGFBP-3 qd provides a more than two-fold higher total exposure. These data indicate that once daily administration of rhIGF-1/rhIGFBP-3 provides prolonged exposure to IGF-I when compared to bid dosing of rhIGF-I.

The mean apparent clearance of circulating IGF-I following administration of rhIGF-1 can be compared to the value following 0.5 mg/kg rhIGF-1/rhIGFBP-3 qd administration because the same four subjects were studied under both conditions. The mean apparent clearance of circulating IGF-I following administration of rhIGF-1 was 0.0206 L/h/kg, whereas the mean clearance following administration of 0.5 mg/kg rhIGF-1/rhIGFBP-3 qd was 0.0074 L/h/kg, thus demonstrating slower elimination of circulating IGF-I following administration of rhIGF-1/rhIGFBP-3.

Upon repeated administration of rhIGF-1/rhIGFBP-3 over a 5-day period to one subject, IGF-I reached steady-state levels within one to two days.

There was a positive correlation between baseline serum ALS level and IGF-I C<sub>max</sub> or AUC following administration of rhIGF-1/rhIGFBP-3 that was not apparent when rhIGF-1 was administered.

IGFBP-3 Pharmacokinetic parameters obtained after chronic dosing of rhIGF-1 or after similar dose administration of rhIGF-1/rhIGFBP-3 are shown in the table below:

**Table 2a. Summary of pharmacokinetic parameters for IGFBP-3 (baseline uncorrected values)**

PK parameters	IGF-1	rhIGF/rhIGFBP3		
	80 ug/kg BID	Dose level		
Daily dose	0 ug/kg	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg
Baseline (ng/mL)	1.30 (0.63) (N=4)	1.30 (0.58) (N=4)	1.08 (0.55) (N=5)	2.15 (-) (N=2)
C <sub>max</sub> (ng/mL)	1.78 (0.85) (N=4)	1.88 (0.82) (N=4)	1.85 (0.69) (N=5)	2.86 (-) (N=2)
T <sub>max</sub> (h)	3.8 (1.5) (N=4)	5.5 (1.7) (N=4)	9.4 (8.3) (N=5)	15 (-) (N=2)
AUC 0-last (ng*hr/mL)	32.41 (15.60) (N=4)	97.26 (53.32) (N=4)	70.66 (57.65) (N=5)	163.6 (-) (N=2)
AUC 0-24 (ng*hr/mL)	32.41 (15.60) (N=4)	36.84 (19.25) (N=4)	36.20 (16.18) (N=4)	59.27 (-) (N=2)

**Table 2b. Summary of pharmacokinetic parameters for IGFBP-3 (baseline corrected values)**

PK parameters	IGF-1	rhIGF/rhIGFBP3		
	80 µg/kg BID	Dose level		
Daily dose	0 µg/kg	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg
Baseline (ng/mL)	-	-	-	-
<b>Cmax</b> (ng/mL)	0.48 (0.35) (N=4)	0.58 (0.26) (N=4)	0.77 (0.33) (N=5)	0.71 (-) (N=2)
<b>Tmax (h)</b>	3.8 (1.5) (N=4)	5.5 (1.7) (N=4)	9.4 (8.3) (N=5)	15 (-) (N=2)
<b>AUC 0-last</b> (ng*hr/mL)	2.26 (1.98) (N=4)	12.86 (12.81) (N=4)	15.13 (7.51) (N=5)	16.53 (-) (N=2)
<b>AUC 0-24</b> (ng*hr/mL)	2.26 (1.98) (N=4)	6.21 (5.04) (N=4)	10.33 (6.33) (N=5)	7.98 (-) (N=2)

**Sponsor's Conclusions:** In this study of five subjects, administration of rhIGF-I/rhIGFBP-3 or rhIGF-I to GHIS subjects restored mean circulating levels of IGF-I to within the normal range. Normalization of IGF-I levels were achieved with a single, once daily dose of rhIGF-I/rhIGFBP-3 in contrast to the twice daily dose required with rhIGF-I. This more favorable dosing regimen is explained by the slower absorption and slower elimination (clearance) of rhIGF-I/rhIGFBP-3 when compared to rhIGF-I alone. These results demonstrate the important role of administered rhIGFBP-3, as well as endogenous ALS, in modulating the systemic exposure of IGF-I. No serious adverse events or instances of hypoglycemia occurred during the study.

**Reviewer's comments:**

One of study objectives was to compare the relative exposure of regular IGF-1 80µg/kg dose of regular IGF-1 to 0.5–2.0 mg/kg of IGF-1/IGFBP-3. The exposure from 80 µg/kg of regular IGF-1 is actually within the range of exposure from 0.5 mg/kg to 2.0 mg/kg of IGF-1/IGFBP-3 complex. However, pre-determined 3 day interval between the doses of 0.5 mg/kg and 1.0 mg/kg apparently was not long enough to let baseline return to predose levels. Sampling points were not frequent enough to reliably determine t1/2. Substantial accumulation at predose, baseline corrected PK may be misleading and not reliable.

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## Study INSM-110-303

**TITLE:** Pharmacokinetic Sub-study for a Phase II/III, Open-Label, Multi-Center Clinical Trial to Evaluate the Safety and Efficacy of an Insulin-Like Growth Factor-1/ Insulin-Like Growth Factor Binding Protein-3 Complex (rhIGF-I/rhIGFBP-3), Administered for 12 Months (Followed by a 12-Month Extension) in Children and Adolescents with Growth Hormone Insensitivity Syndrome (GHIS) such as Laron Syndrome.

### INVESTIGATOR:

### OBJECTIVES:

The objectives for this Pharmacokinetic Sub-study were to further characterize the pharmacokinetics of rhIGF-I and rhIGFBP-3 following a single dose of rhIGF-I/rhIGFBP-3 in GHIS subjects and to compare the pharmacokinetic profiles for drug products manufactured at two different manufacturing facilities.

### PHARMACOKINETIC SUB-STUDY DESIGN:

This study is a prospective, open-label, multi-center Pharmacokinetic Sub-study to further characterize the pharmacokinetics of rhIGF-I and rhIGFBP-3 following a single dose of 1.0 mg/kg rhIGF-I/rhIGFBP-3 in OHS subjects and compare the pharmacokinetic profiles for drug products manufactured at two different manufacturing facilities. Subjects first received a single dose of 1.0 mg/kg rhIOF-JJrhIGFBP-3 Development

Drug Product (DDP, Insmad, Santa Clara, CA). Following a minimum 7-day washout period, during which they received no treatment, subjects received a single dose of 1.0 mg/kg rhIGF-IJrhIGFBP-3 Commercial Drug Product (CDP#1, Avecia, Billingham, UK). Serum samples were collected 0, 6, 9, 12, 15, 18, 24, 36, 48, and 60 hours following each treatment dose for measurement of IGF-I, IGF-II, IOFBP-3, and ALS serum levels.

### NUMBER OF SUBJECTS IN THE PHARMACOKINETIC SUB-STUDY:

PLANNED: Up to 10      ENROLLED: 4      COMPLETED: 4      ANALYZED: 4

### DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Subjects enrolled in this sub-study came from the 2nd cohort of subjects enrolled in Clinical Study INSM-110-303 (Cohort #2) and had to specifically agree to participate in this Pharmacokinetic Sub-study. The subjects had to have a diagnosis of GHIS, such as Laron syndrome. Inclusion criteria included age 2-18 years; pre-pubertal; height standard deviation score (SDS)  $\leq -3$  for age; basal IGF-I SDS  $\leq -2$  for age; peak stimulated growth hormone (GM)  $> 13.3 \mu\text{g/L}$ ; and basal IGFBP-3 SDS  $\leq 1$  for age. The subjects had to have a documented height velocity assessment from the previous 12 months and be willing to give informed consent/assent. Exclusion criteria included bone age  $> 12$  years for girls or 14 years for boys; malignancy; diabetes; treatment with rhIGF-I, GH or other experimental drug within the previous 3 years, 6 months or 30 days, respectively; clinically significant neuropathy, nephropathy, retinopathy, or other microvascular /macrovascular disease; AST or ALT greater than or equal to 2 times the normal reference range; serum creatinine greater than  $150 \mu\text{mol/L}$  ( $1.70 \text{ mg/dL}$ ); previous treatment with GnRH analogs or chronic systemic corticosteroid use; and any other condition or therapy that, in the investigator's opinion, may pose a risk to the subject or interfere with the subject's ability to be compliant with this protocol.

**TEST PRODUCT, DOSE, MODE OF ADMINISTRATION:**

The test product was rhIGF-I/rhIGFBP-3 in 50mM sodium acetate, 105 mM sodium chloride, pH 5.5.

DDP: Development scale drug product manufactured in Santa Clara, CA.

CDP# 1: Commercial scale drug product manufactured at Avecia in Billingham, UK

**DURATION OF TREATMENT:**

The pharmacokinetic sub-study consists of 2 doses of study medication (one dose of DDP and one of CDP# 1) separated by an approximately one week washout period.

**PHARMACOKINETIC ASSESSMENT METHODS:**

Serum IGF-I, IGFBP-3, and ALS levels were assessed at all time points and are listed and summarized by drug product (CDP#1, DDP). The following pharmacokinetic parameters for a single dose of rhIGF-I/rhIGFBP-3 are calculated (with and without baseline-correction) and summarized by drug product for IGF-I and IGFBP-3 using descriptive statistics:

- \* C<sub>max</sub>: Maximum serum concentrations
- \* T<sub>max</sub>: Time of the maximum concentrations
- \* AUC(0-24): Area under the serum concentration-time curves from time zero to 24 hours post-dose
- \* AUC(0-60): Area under the serum concentration-time curves from time zero to 60 hours post-dose
- \* AUC(0-t<sub>last</sub>): Area under the serum concentration-time curves from time zero to last measurement
- \* AUC(0-∞): Area under the serum concentration-time curves from time zero to infinity
- \* t<sub>1/2</sub>: Elimination half-life (calculated only if at least 2 consecutive descending time points after T<sub>max</sub>)
- \* K<sub>el</sub>: Elimination rate constant (calculated only if at least 2 consecutive descending time points after T<sub>max</sub>)
- \* CL/F: Apparent clearance estimated as dose/AUC(0-t).
- \* V<sub>d</sub>/F: Apparent volume of distribution estimated as dose/(K<sub>el</sub>\* AUC(0-t)).

**STATISTICAL METHODS:**

Due to the small number of subjects who participated in the Pharmacokinetic Sub-study, drug products were compared by examining descriptive statistics and individual subject data. This study was not designed or powered to provide a formal bioequivalence assessment.

**SUMMARY OF RESULTS AND CONCLUSIONS:**

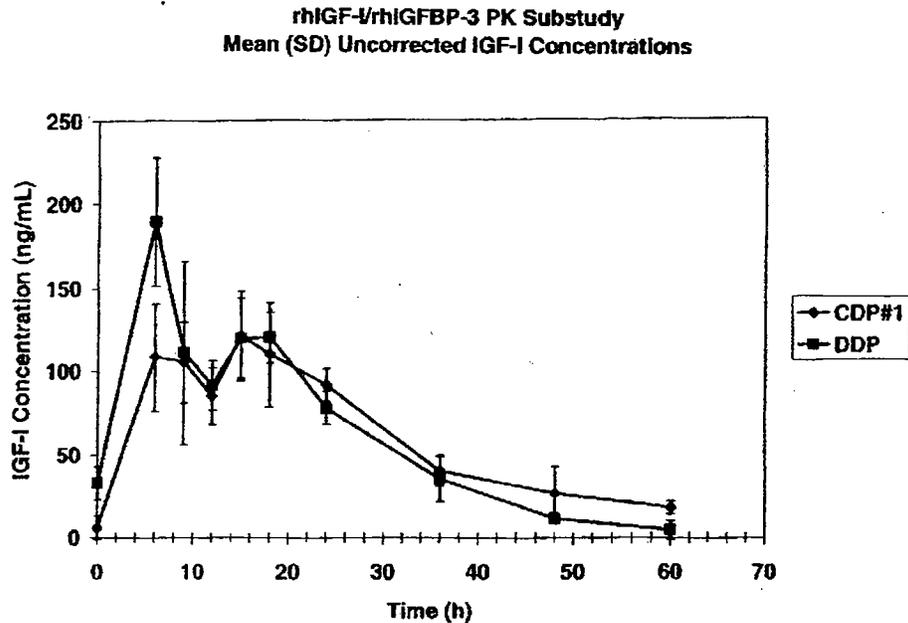
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**IGF-I Results:**

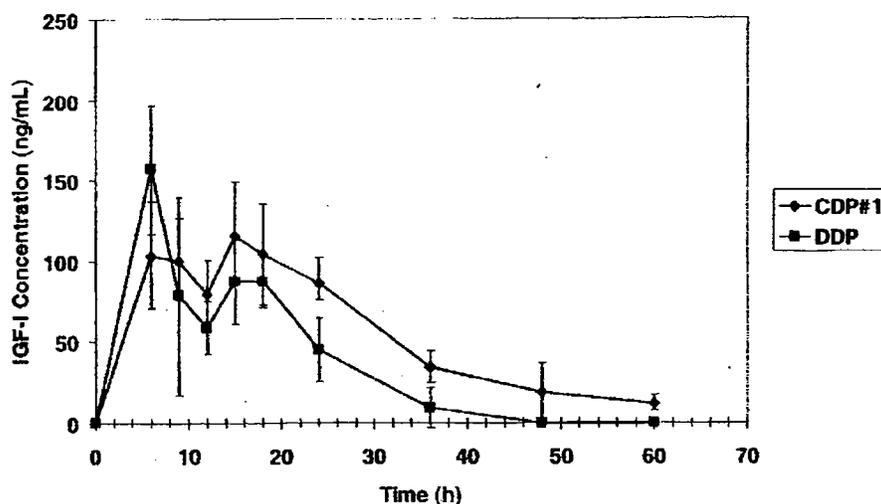
IGF-I Pharmacokinetics		Uncorrected IGF-I		Baseline-Corrected IGF-I	
rhIGF-I/rhIGFBP-3 Product (1.0 mg/kg)		DDP	CDP#1	DDP	CDP#1
C <sub>max</sub> (ng/mL)	Mean (SD)	190 (38)	133 (19)	157 (40)	127 (25)
	N	4	4	4	4
T <sub>max</sub> (h)	Mean (SD)	6.0 (0.0)	11.3 (6.2)	6.0 (0.0)	11.3 (6.2)
	N	4	4	4	4
AUC <sub>0-24</sub> (ng hr/mL)	Mean (SD)	2696 (463)	2215 (373)	1908 (552)	2073 (464)
	N	4	4	4	4
AUC <sub>0-Tlast</sub> (ng hr/mL)	Mean (SD)	3742 (540)	3654 (237)	2202 (726)	3299 (643)
	N	4	4	4	4
AUC <sub>0-66</sub> (ng hr/mL)	Mean (SD)	3786 (592)	3654 (237)	2291 (752)	3299 (643)
	N	4	4	4	4
AUC <sub>0-∞</sub> (ng hr/mL)	Mean (SD)	3968 (578)	3994 (222)	2337 (859)	3506 (794)
	N	4	4	4	4
Half-Life (h)	Mean (SD)	13.7 (6.8)	13.4 (2.7)	5.1 (3.0)	10.7 (5.4)
	N	4	4	4	4
Cl/F mL/hr/kg	Mean (SD)	53.76 (7.22)	52.76 (2.94)	98.46 (31.79)	62.40 (14.43)
	N	4	4	4	4
Vz/F mL/kg	Mean (SD)	1070 (581)	1018 (188)	634 (145)	885 (349)
	N	4	4	4	4

\*Calculations for AUC<sub>(0-Tlast)</sub>, AUC<sub>(0-60)</sub>, AUC<sub>(0-∞)</sub>, half-life, Cl/F and Vz/F were affected by differences in baseline IGF-I levels.

**Figure 1. Mean (SD) Serum IGF-I Concentration-Time Profiles.**  
(Top and bottom panels provide mean uncorrected and baseline-corrected data, respectively.)



**rhIGF-1/rhIGFBP-3 PK Substudy  
Mean (SD) Corrected IGF-1 Concentrations**



**Effect of Differences in Apparent Baseline IGE-I Levels**

The IGF-I concentrations following administration of CDP#1 followed an expected concentration profile, with levels in the tail of the curve reaching the baseline (time 0) level. In contrast, the mean serum IGF-I level just prior to administration of DDP (time 0) was higher than the mean levels 48 and 60 hours following administration of DDP. This difference in apparent baseline levels within subjects can have a substantial effect on cross-treatment comparisons of baseline-corrected pharmacokinetic parameters. For the DDP treatment, unlike CDP#1, the baseline-corrected levels were negative (and set to 0 for analysis) for a majority of each subject's sample time points beyond 36 hours. This resulted in an apparent underestimation of AUC(0-tLast), AUC(0-60), AUC(0-∞), half-life and volume of distribution and an apparent overestimation of clearance when using baseline-corrected levels for the DDP treatment and thus these parameters were not considered relevant for the comparison of pharmacokinetic profiles for CDP#1 and DDP.

**IGF-I Absorption and Maximum Exposure (Tmax, Cmax)**

Two absorption peaks for IGF-I were observed following all treatment administrations for both drug products. The overall (combining data from both drug products) mean time to peak concentration was 7.5 and 18.75 hours for the first and second peaks respectively. After administration of DDP, all subjects had a Tmax that corresponded with the first absorption peak (at 6 hours). After administration of CDP#1, two subjects peaked at 6 hours while the other two subjects showed maximum concentrations during the second absorption peak (at 15 and 18 hours). The uncorrected Cmax values for treatments DDP and CDP#1 were 190 and 133 ng/mL and the baseline-corrected values were 157 and 127 ng/mL, respectively. In general, the absorption and maximum concentration profiles for the DDP and CDP#1 treatments were comparable.

**IGF-I Exposure (AUC(0-24), AUC(0-60), AUC(0-tLast), and AUC(0-∞))**

The mean (SD) IGF-I AUC(0-∞) (calculated using uncorrected concentration levels) for DDP and CDP#1 were essentially the same at 3968 (578) and 3994 (222) hr\*ng/mL, respectively. AUC(0-24), AUC(0-60), AUC(0-tLast) were also comparable for the two treatments.

**IGF-I Elimination Half-life, Clearance and Volume of Distribution:**

The mean half-life (calculated using uncorrected concentration levels) following administration of 1.0 mg/kg rhIGF-I/rhIGFBP-3, was between 13 and 14 hours for both CDP#1 and DDP.

The mean (SD) apparent clearance values of IGF-J (calculated using uncorrected concentration levels) were 52.8 (2.9) and 53.8 (7.2) mL/hr/kg for CDP#1 and DDP, respectively.

The mean (SD) apparent volume of distribution values of IGF-I (calculated using uncorrected concentration levels) were 1018 (188) and 1070 (581) mL/kg for CDP#1 and DDP, respectively.

**IGFBP-3 Results:**

IGFBP-3 Pharmacokinetics		Uncorrected IGFBP-3		Baseline-Corrected IGFBP-3	
rhIGF-I/rhIGFBP-3 Product (1.0 mg/kg)		DDP	CDP#1	DDP	CDP#1
C <sub>max</sub> (ng/mL)	Mean (SD)	1453 (278)	1574 (401)	857 (184)	920 (603)
	N	4	4	4	4
T <sub>max</sub> (h)	Mean (SD)	12.0 (5.5)	19.5 (9.0)	12.0 (5.5)	19.5 (9.0)
	N	4	4	4	4
AUC <sub>0-24</sub> (ng hr <sup>-1</sup> /mL)	Mean (SD)	26882 (3218)	26907 (2748)	12585 (3564)	11344 (5871)
	N	4	4	4	4
AUC <sub>0-tLast</sub> (ng hr <sup>-1</sup> /mL)	Mean (SD)	53538 (7342)	62525 (8352)	18748 (4103)	23706 (13352)
	N	4	4	4	4
AUC <sub>0-60</sub> (ng hr <sup>-1</sup> /mL)	Mean (SD)	53538 (7342)	62525 (8352)	19282 (3560)	23834 (13149)
	N	4	4	4	4
AUC <sub>0-∞</sub> (ng hr <sup>-1</sup> /mL)*	Mean (SD)	86671 (33178)	123019 (65283)	20586 (2307)	37416 (2181)
	N	4	2	4	2
Half-Life (h)*	Mean (SD)	35.6 (19.2)	54.1 (31.6)	9.9 (4.0)	9.0 (2.2)
	N	4	2	4	2
Cl/F mL/hr/kg*	Mean (SD)	10.17 (3.72)	7.47 (3.97)	38.73 (4.35)	21.14 (1.23)
	N	4	2	4	2
Vz/F mL/kg*	Mean (SD)	444 (94)	492 (32)	560 (257)	278 (84)
	N	4	2	4	2

\*Baseline-corrected calculations for AUC<sub>(0-∞)</sub>, half-life, Cl/F and Vz/F based on data from only 2 subjects.

**IGFBP-3 Absorption and Maximum Exposure (T<sub>max</sub>, C<sub>max</sub>)**

Two absorption peaks for IGFBP-3 were observed following 3 of the 4 administrations of each drug product. For the concentration profiles with 2 peaks, the overall (combining data from both drug products) mean time to peak concentration was 7.5 and 17 hours for the first and second peaks, respectively. The uncorrected mean C<sub>max</sub> values were 1574 and 1453 for CDP#1 and DDP, respectively. The absorption and maximum exposure profiles were comparable for both drug products.

**IGFBP-3 Exposure [AUC(0-24), AUC(0-60), AUC(0-tLast), and AUC(0-∞)]**

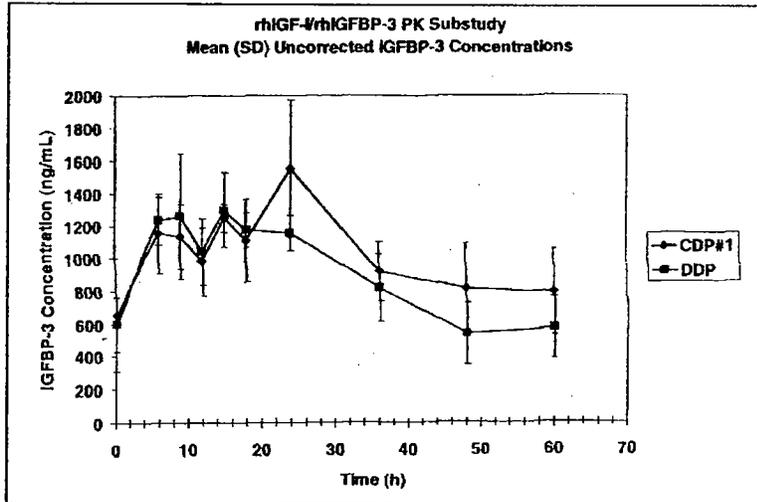
Area under the serum IGFBP-3 concentration versus time curve (AUC) is used as a measure of total exposure. Because half-life was inestimable for 2 of the 4 subjects and the corresponding AUC(0-∞) values were missing, the IGFBP-3 AUC(0-∞) values could not be used to compare the extent of IGFBP-3 exposure between treatments DDP and CDP#1. AUC(0-24), AUC(0-60), AUC(0-tLast) are not affected by half-life. The mean (SD) IGFBP-3 AUC estimates (calculated

using uncorrected concentration levels) were comparable for the two treatments (DDP vs. CDP#1) at 26882 (3218) vs. 26907 (2748), 53538 (7342) vs. 62525 (2352) and 53538 (7342) vs. 62525 (8352) hr\*ng/mL for AUC(0-24), AUC(0-60), AUC(0-tLast), respectively.

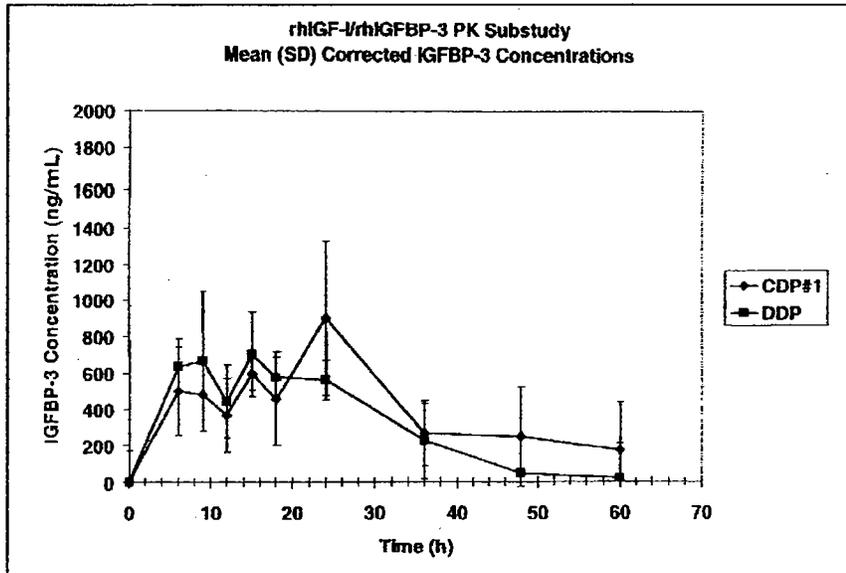
**IGFBP-3 Elimination Half-life, Clearance and Volume of Distribution:**

Since half lives, clearance and volume of distribution could only be calculated in two of four subjects receiving CDP#1 a meaningful comparison of mean half lives, clearance and volume of distribution for IGFBP-3 was not possible.

Figure 2. Mean (SD) Actual Serum IGFBP-3 Concentration-Time Profiles.(Top and bottom panels provide mean uncorrected and baseline-corrected data, respectively.)



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**Sponsor's Conclusions:**

Four subjects with ages ranging from 4 to 14 years successfully completed this Pharmacokinetic Sub-study in which single subcutaneous injections of 1.0 mg/kg rhIGF-I/rhIGFBP-3 from drug products produced at two different manufacturing facilities were administered. Both drug products produced IGF-I levels within the normal range, IGFBP-3 levels approaching the normal range and pharmacokinetic profiles for IGF-I and IGFBP-3 that were comparable to one another.

Two absorption peaks for IGF-I were observed following all treatment administrations for both drug products. The overall mean time to peak concentration was 7.5 and 18.75 hours for the first and second peaks, respectively. The mean AUC(0-∞), half-life, apparent clearance and apparent volume of distribution calculated using uncorrected IGF-I levels, was 3994 and 3968 hr\*ng/mL, 13.4 and 13.7 hours, 52.8 and 53.8 mL/hr/kg, and 1018 and 1070 mL/kg for CDP#1 and DDP, respectively.

Two absorption peaks for IGFBP-3 were observed following 3 of the 4 administrations of each drug product. For the concentration profiles with 2 peaks, the overall mean time to peak concentration was 7.5 and 17 hours for the first and second peaks, respectively. The mean AUC(0-24) and AUC(0-tLast), calculated using uncorrected IGFBP-3 levels, was 26907 and 26882 hr\*ng/mL, and 62525 and 53538 hr\*ng/mL for CDP#1 and DDP, respectively.

In healthy subjects, the vast majority of naturally circulating IGF-I exists in the form of a ternary complex of equimolar amounts of IGF (IGF-I and IGF-II), IGFBP-3 and ALS with a very small percentage of IGF-I in the free unbound state. Although the GHIS subjects in this study had no detectable ALS the equimolar relationship between IGF (IGF-I and IGF-II) and IGFBP-3 was present and comparable following both drug products. This result suggests that rhIGFBP-3, when administered in the form of rhIGF-I/rhIGFBP3, may play a role in the regulation of bioactivity of IGF-I even in the absence of ALS.

***Reviewer's comments:***

DDP was used in clinical trial Cohort 1 with 19 patients. CDP#1 was used in clinical trial Cohort #2 with 10 patients and a sub study with 4 patients for pharmacokinetics. From PK comparison, CDP#1 drug products exhibited about 50% more in AUC(0-last) and doubled the t<sub>1/2</sub> from 5.1 hours to 10.7 hours. These two drug products are not comparable based on their pharmacokinetic performance. Since CDP#1 drug products were used Clinical trial Cohort #2 with 10 patients, the comparability between these two drug products in clinical efficacy and safety will be judged by the medical reviewer.

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**Study 9601**

**Title:** A Phase I Study of the Safety and Pharmacokinetics of Single Intravenous Doses of Recombinant Human Insulin Like Growth Factor-I/Insulin Like Growth Factor Binding Protein-3 (rhIGF-1/IGFBP-3)

**Principal Investigator:** \_\_\_\_\_

**Study Center:** \_\_\_\_\_

**Study Period:** First Subject Screened: 7 May 1996, Last Subject Completed: 24 June 1996.

**Phase of Development:** Phase I

**Objective:** To evaluate for the first time in humans, the safety, tolerability, and pharmacokinetics of single intravenous infusions of rhIGF-1/IGFBP-3 over a range of doses.

**Methodology:** This was a randomized, open-label, sequential cohort dose escalation, single intravenous infusion bioequivalence study.

**Number of Subjects:** Twelve subjects were enrolled and completed the study. Of the 12 subjects enrolled, 6 (50%) were female and 6 (50%) were male. Nine (75%) of the subjects were Caucasian, 2(17%) were Hispanic, and 1(8%) was black. The mean age of the subjects was 26.3 years, with a range of 20 to 48 years.

**Diagnosis and Main Criteria for Inclusion:** Subjects were healthy, nonsmoking adults (male or female) between the ages of 18 and 60 years who satisfied all screening requirements.

**Test Product, Dose and Mode of Administration, Batch Numbers:** Recombinant hIGF-1/IGFBP-3 was administered in a sequential-cohort dose escalation. Three subjects in each treatment cohort received the active drug. All doses were administered over a 15-minute intravenous infusion. The following doses were administered during the study:

- A a single dose of 0.3 mg/kg IV rhIGF-1/IGFBP-3 (Lot No.7028)
- B a single dose of 1.0 mg/kg IV rhIGF-1/IGFBP-3 (Lot No.7028)
- C a single dose of 3.0 mg/kg IV rhIGF-1/IGFBP-3 (Lot No. 7028)
- D a single dose of 6.0 mg/kg IV rhIGF-1/IGFBP-3 (Lot No.7028)

**Duration of Treatment:** 1 day, single dose

**CRITERIA FOR EVALUATION:**

**Pharmacokinetics:** AUC(0-48), AUC(0-inf), Cmax, Tmax, T½, Cl, V

**Safety:** Vital signs (supine systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral temperature), routine laboratory data, medical history, physical examination findings, ECG evaluations, and adverse events were assessed.

**Statistical Methods:**

Summary statistics, including mean, standard deviation (SD), maxima, and minima were computed for raw and derived pharmacokinetic parameters; differences in mean pharmacokinetic parameters were tested for differences due to dose group analysis of variance (ANOVA) using the general linear models (GLM) procedure of SAS; dose proportionality was assessed by one-way ANOVA.

**Pharmacokinetic Results:**

Summary of IGF-I Pharmacokinetic Parameters - Baseline Corrected

Parameter	Mean ± SD			
	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg	6.0 mg/kg
AUC <sub>(0-48)</sub> (ng•hr/mL)	7794 ± 2571	11207 ± 1915	19001 ± 5897	23146 ± 2979
AUC <sub>(0-inf)</sub> (ng•hr/mL)	8606 ± 2660	11377 ± 2888	22351 ± 6801	23592 ± 3274
C <sub>max</sub> (ng/mL)	925 ± 127	3400 ± 175	7145 ± 754	15967 ± 3148
T <sub>max</sub> (hr)	0.00 ± 0.00	0.05 ± 0.05	0.03 ± 0.05	0.06 ± 0.10
K <sub>elim</sub> (1/hr)	0.049 ± 0.007	0.066 ± 0.011	0.048 ± 0.025	0.082 ± 0.020
T <sub>1/2</sub> (hr)	14.3 ± 2.1	10.6 ± 1.6	17.1 ± 7.8	8.8 ± 1.9
Cl (mL/hr)	473 ± 120	1171 ± 273	2049 ± 811	3733 ± 466
V(mL)	9924 ± 3629	18231 ± 6538	56608 ± 43399	46545 ± 4926
Cl (mL/hr/kg)	7.4 ± 2.1	19.3 ± 5.2	30.2 ± 10.0	54.1 ± 7.5
V (ml/kg)	154 ± 52	299 ± 111	817 ± 604	687 ± 184

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Summary of IGFBP-3 Pharmacokinetic Parameters - Baseline Corrected

Parameter	Mean ± SD			
	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg	6.0 mg/kg
AUC <sub>(0-48)</sub> (ng.hr/mL)	16310 ±5577	45788 ± 7395	100484 ±49346	126410 ±12168
AUC <sub>(0-inf)</sub> (ng.hr/mL)	17413±189	57631 ±3179	169338 ±154755	126591 ±11496
C <sub>max</sub> (ng/mL)	4300 ±854	42133 ±11491	62967 ± 1097	125267 ±6525
T <sub>max</sub> (hr)	0.05 ± 0.05	0.03 ± 0.05	0.05 ± 0.05	0.08 ± 0.00
K <sub>elim</sub> (1/hr)	0.154 ±0.006	0.103 ±0.058	0.102 ±0.121	0.138 ±0.040
T <sub>½</sub> (hr)	4.52 ±0.18	9.67 ± 7.96	16.88 ±14.54	5.31 ±1.57
Cl (mL/hr)	835 ± 69	839 ± 81	1602 ±1136	2603 ±257
V(mL)	5430 ±228	12326 ±11293	23155 ±15482	19686 ±4664
Cl (mL/hr/kg)	13.8 ±0.1	13.7 ±0.8	22.9 ± 15.6	37.7 ± 3.6
V (mL/kg)	90 ±5	187 ±146	340 ±198	293 ±115

#### Summary of Pharmacokinetic Results:

The AUG, C<sub>max</sub>, CL, and V values for IGF-1 and IGFBP-3 appeared to increase as the dose level increased. However, the increases in the IGF-1 AUC and C<sub>max</sub> values were not shown to be proportional to the increases in dose.

Although the increase in the AUG values for IGFBP-3 was statistically shown to be proportional to the increasing dose, these non-significant effects were affected by large AUG values seen for Subject 009, which produced high variation in AUC. This variation may have decreased the power of the ANOVA to a level that would have prevented the detection of any underlying differences in dose-normalized AUG.

Subject 009 had nonzero concentrations at all time points out to 48 hours, which did not occur for most subjects. These concentrations produced a large value of AUC(0-48), as well as a long estimated half-life, which subsequently resulted in a high AUG(0-inf.). The AUC values for Subject 009 (3.0 mg/kg treatment cohort) were larger than any AUC values for any subject in the 6.0 mg/kg treatment cohort.

#### Sponsor's Conclusions:

There was a statistically significant dose effect on some of the pharmacokinetic parameters. Values for AUC<sub>0-48</sub>, AUC<sub>0-inf.</sub>, C<sub>max</sub>, CL, and V tended to increase with the increasing dose. The T<sub>max</sub> tended to be unaffected by dose level. Estimates of elimination rate and half-life did not differ significantly between dose levels. Dose limiting adverse events, related to acute hypoglycemia and acute hypophosphatemia were observed in the 6.0 mg/kg dose group. Based on the results of this study, the maximum tolerated single dose of rhIGF-I/IGFBP-3 administered intravenously over 15 minutes is 3 mg/kg.

**Reviewer's comments:**

C<sub>max</sub> and AUC appear to increase with dose increases, but not proportionally. However, t<sub>1/2</sub> varied so much from 17.1 hours at dose of 3.0 mg/kg down to 8.8 hours at dose of 6.0 mg/kg for IGF-1 and from 17 hours to 5.3 hours for IGFBP-3. It is difficult to explain why t<sub>1/2</sub> decreases with dose increases.

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## Study 9602

**Title:** A Phase I Study of the Safety and Pharmacokinetics of Multiple Intravenous Doses of Recombinant Human Insulin Like Growth Factor-I/Insulin Like Growth Factor Binding Protein-3 (rhJGF-1/IGFBP-3).

**Principal Investigator:** \_\_\_\_\_

**Study Center:** \_\_\_\_\_

**Study period:** First Subject Screened: 24 June 1996; Last Subject Completed: 17 August 1996

**Phase of Development:** Phase I

**Objectives:** To evaluate the safety and pharmacokinetics of daily intravenous infusions of rhIGF-1/IGFBP-3 for six consecutive days over a range of doses, in healthy, normal subjects  
**Methodology:** This was a randomized, double-blind, placebo-controlled, sequential cohort dose escalation, daily intravenous infusion study.

**Number of Subjects:** (Planned and Analyzed): Eighteen subjects (6 subjects per dose group) were projected for enrollment in the study. Nineteen subjects were enrolled in the study and were evaluable for safety. Of these, 17 subjects completed the study.

Eleven of the 17 subjects who completed the study received the active drug and a total of seven subjects (2 subjects per dose group and Subject 009 who discontinued the study) received placebo. Subject 009 discontinued the study due to non-serious adverse events (moderate erythema at the dose site and mild rash). Both of these events were considered by the investigator to be probably related to the study medication. Subject 018 dropped out of the study after he withdrew consent. The 11 subjects who received the active drug and completed the study were included in the statistical analysis of the pharmacokinetic data. Of the 19 subjects enrolled, 10 (53%) were female and 9 (47%) were male. Fifteen (79%) were Caucasian, 3 (16%) were Hispanic, and 1(15%) was black. The mean age of the subjects was 34 years with a range of 19 to 60 years.

**Diagnosis and Main Criteria for Inclusion:** Subjects were healthy, nonsmoking adults (male or female) between the ages of 18 and 60 years who satisfied all screening requirements.

### **Test Product, Dose and Mode of Administration, Batch Numbers:**

Recombinant hJGF-1/IGFBP-3 was administered in a sequential-cohort dose escalation. Four subjects in each treatment cohort received the active drug and two subjects received placebo. All doses were administered over a 15-minute intravenous infusion. The following doses were administered during the study:

A. 0.3 mg/kg IV rhIGF-1/IGFBP-3 (Lot No. 7028) or placebo (Lot No. 7029) once a day for 6 days.

B. 1.0 mg/kg IV rhIGF-1/IGFBP-3 (Lot No. 7028) or placebo (Lot No. 7029) once a day for 6 days.

C. 3.0 mg/kg IV rhIGF-1/IGFBP-3 (Lot No. 7028) or placebo (Lot No. 7029) once a day for 6 days.

Duration of Treatment: IGF-1/IGFBP-3 was administered once a day for a total of 6 days.

Reference Therapy, Dose and Mode of Administration, Batch Number:

**Placebo solution 0 mg/mL W (Lot No.7029)**

**CRITERIA FOR EVALUATION:**

**Pharmacokinetics:** AUC<sub>0-24</sub>, AUC<sub>0-inf.</sub>, (Day 1), K<sub>e</sub>, C<sub>max</sub>, T<sub>1/2</sub>, CL, and V on Day 1 and Day 6

**Safety:** Vital signs (supine systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral temperature), routine laboratory data, adverse events, physical examinations, and ECU; measures of central tendency (mean and median) and variance (standard error, standard error of the mean) were computed and examined for any dose-related trends.

**Statistical Methods:**

Dose level and gender differences: ANOVA

Differences in pharmacokinetic parameters between Days 1 and 6: paired t-tests  
Dose proportionality of pharmacokinetic parameters: one-way ANOVA  
Comparison of mean daily nitrogen balance: ANOVA.

Differences in change-from-baseline values of insulin and insulin c-peptide: Student's t- test

Treatment versus placebo differences in change-from-baseline values of growth hormone: Wilcoxon rank-sum test.

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**Pharmacokinetic Results:**

**Summary of IGF-1 Pharmacokinetic Parameters - Day 1<sup>a</sup>**

Parameter	Mean ± SD			
	Placebo N=5	0.3 mg/kg N=4	1.0 mg/kg N=4	3.0 mg/kg N=4
AUC <sub>0-24</sub> (ng•hrs/mL)	394±421	6117 ±841	8723 ±1480	15628 ±4047
AUC <sub>0-inf</sub> (ng•hrs/mL)	-	7465 ±1300	10785 ±2204	18216 ±5608
C <sub>max</sub> (ng/mL)	290 ±104	1204 ±162	3052 ± 434	6785 ± 962
T <sub>max</sub> (hr)	1.15±0.80	0.08 ±0.12	0.06 ±0.04	0.10 ±0.08
K <sub>elim</sub> (1/hr)	-	0.074 ±0.015	0.069 ± 0.009	0.078 ± 0.005
T <sub>1/2</sub> (hr)	-	9.70 ±2.00	10.23 ±1.25	8.90 ±0.61
Cl (mL/hr)	-	548 ± 107	1296 ±459	2690 ± 823
V (mL)	-	7493 ± 1072	18589 ±4251	34911 ±12329
Cl (mL/hr/kg)	-	8.62 ±1.38	20.11 ±4.22	36.62 ± 8.84
V (mL/kg)	-	119±21	292 ± 38	473 ±131

<sup>a</sup>Data taken from Table 2.1 in Study report submitted September 11, 2003

-No pharmacokinetic parameters relating to the elimination phase were calculated for the placebo group

**Summary of IGF-1 Pharmacokinetic Parameters - Day 6a**

Parameter	Mean ± SD			
	Placebo N=5	0.3 mg/kg N=4	1.0 mg/kg N=4	3.0 mg/kg N=3
AUC <sub>0-24</sub> (ng•hrs/mL)	350 ± 454	6411±1539	8086 ±1765	13069 ±2802
C <sub>max</sub> (ng/mL)	274 ± 91	1293 ± 126	2886 ± 375	6778 ±1174
T <sub>max</sub> (hr)	0.95 ± 0.72	0.04 ±0.05	0.02 ± 0.04	0.11 ±0.05
K <sub>elim</sub> (1/hr)	-	0.049 ±0.019	0.050 ± 0.022	0.058 ± 0.008
T <sub>1/2</sub> (hr)	-	16.37 ±7.89	16.26 ±7.47	12.14 ±1.89
Cl (mL/hr)	-	655 ±190	1718 ±563	3693 ±1036
V (mL)	-	14875 ± 5654	37459 ±12548	66011 ±26594
Cl (mL/hr/kg)	-	10.3 ±2.6	26.9 ± 5.9	49.6 ± 9.5
V (mL/kg)	-	236 ± 93	587 ±150	877 ± 265

Summary of IGFBP-3 Pharmacokinetic Parameters - Day 1<sup>a</sup>

Parameter	Mean ± SD			
	Placebo N=5	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
AUC <sub>0-24</sub> (ng•hrs/mL)	1134 ±1338	19788 ±6435	25067 ± 4424	73218 ±21245
AUC <sub>0-inf</sub> (ng•hrs/mL)	-	21693 ±7518	25434 ± 4558	76050 ±221 79
C <sub>max</sub> (ng/mL)	3280 ± 327	8075 ± 685	15750 ±221 7	69250 ±18392
T <sub>max</sub> (hr)	5.78 ±10.02	0.02 ± 0.04	0.06 ± 0.04	0.08 ± 0.00
K <sub>elim</sub>	-	0.226 ±0.140	0.196 ±0.055	0.139 ±0.067
T <sub>1/2</sub> (hr)	-	3.98 ± 2.06	3.79 ±1.22	5.64 ±1.85
Cl (mL/hr)	--	785 ±359	2066 ± 739	2431 ± 808
V(mL)	-	391 9 ±1366	11163±4394	19061 ±8085
Cl	-	12.64 ±6.62	31.91 ±6.37	33.06 ± 8.80
V (mL/kg)	-	61 ±19	171 ±53	264±111

a Data taken from Table 3.1 in Study Report submitted September 11, 2003

-- No pharmacokinetic parameters relating to the elimination phase were calculated for the placebo group

Summary of IGFBP-3 Pharmacokinetic Parameters - Day 6<sup>a</sup>

Parameter	Mean * SD			
	Placebo N=5	0.3 mg/kg N=4	1.0 mg/kg N=4	3.0 mg/kg N=3
AUC <sub>0-24</sub> (ng•hrs/mL)	116±239	14386 ±5241	2021 9 ±2642	51193 ±23159
C <sub>max</sub> (ng/mL)	3120 ±370	8025 ±1011	14500 ±1000	64000 ± 29597
T <sub>max</sub> (hr)	5.45 ±10.40	0.02 ±0.04	0.02 ± 0.04	0.06 ±0.05
K <sub>elim</sub> (1/hr)	--	0.190 ±0.080	0.284 ±0.1 37	0.488 ± 0.527
T <sub>1/2</sub> (hr)	-	4.14 ±1.62	2.77 ±0.93	3.07 ± 2.63
Cl (mL/hr)	-	1151 ±400	2516 ± 592	3908 ±1674
V(mL)	-	6818 ±3611	9561 ± 2340	13254 ±7494
Cl (mL/hr/kg)	-	18.3 ±6.8	39.6 ±5.1	51 .9 ±18.6
V (mL/kg)	-	106 ±50	154 ±42	187±113

<sup>a</sup>Data taken from Table 3.2

--No pharmacokinetic parameters relating to the elimination phase were calculated for the placebo group

Statistically significant dose level differences were seen among the pharmacokinetic parameters. The values of AUC and C<sub>max</sub> increased with dose level on both Day 1 and Day 6. However, the increases were not found to be proportional to the increases in dose. T<sub>max</sub> was seen to be independent of dose level.

Examination of mean values of Kelim and Tmax shows similar values across dose levels for IGF-1 on both Days 1 and 6. The IGF-1 half-life of 12-16 hours estimated from Day 6 data indicates that the terminal phase on Day 1 may not have been completely captured in the 24-hour sampling period, resulting in the dissimilar values on the two days. For IGFBP-3, Day 6 values of Kelim and T<sub>1/2</sub> are similar to those for Day 1. The estimated IGFBP-3 half-life of 3-4 hours gives a good indication that the elimination phase occurs within 24 hours, resulting in the similar values on Days 1 and 6.

**Sponsor's conclusions:**

Statistically significant dose level differences were seen among the pharmacokinetic parameters. The values of AUC and Cmax increased with dose level on both Day 1 and Day 6. However, the increases were not found to be proportional to the increases in dose. Tmax was seen to be independent of dose level.

**Reviewer's comments:**

The PK results from this multiple IV dosing study appear to be consistent between Day 1 and Day 6. Overall, this IV PK study is more reliable to retrieve PK parameters for IGF-1/IGFBP-3 than the previous single dose IV study.

**APPEARS THIS WAY  
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## Study 9604

**Title:** A Phase I Study of the Safety and Pharmacokinetics of Continuous Subcutaneous Infusion of Recombinant Human Insulin Like Growth Factor-I/Insulin Like Growth Factor Binding Protein-3 (rhIGF-IIIGFBP-3) for Seven Days in Healthy Elderly Female Subjects.

**Principal Investigator:** \_\_\_\_\_

**Study Center:** \_\_\_\_\_

**Study period:** Date of first enrollment: 05-Nov-1996, Date of last completed: 19-Dec-1996

**Phase of Development:** Phase I

**Objectives:** The objective of the study was to evaluate the safety and pharmacokinetics of continuous infusion of rhIGF-IIIGFBP-3 for seven consecutive days over a range of doses in healthy elderly female subjects.

**Methodology:** This was a randomized, double blind, placebo controlled, sequential cohort study involving three dose administration levels (0.5, 1.0, and 2.0 mg/kg/day). Twelve healthy females, age 55-70 were enrolled into three dose groups, four subjects per dose level (three drug, one placebo).

**Number of Subjects (planned and analyzed):** Twelve (12) subjects were enrolled in the study. A total of 12 subjects completed the study. All 12 subjects were included in pharmacokinetic and safety analyses. All 12 subjects were female ranging in age from 55 to 70 years; the mean age was 65 years. Seven (7) subjects were Caucasian and five (5) were Hispanic.

**Diagnosis and Main Criteria for Inclusion:** All subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers. Enrolled subjects met inclusion and exclusion criteria reflective of the fact that they were normal, healthy volunteers.

**Test Product, Dose and Mode of Administration, Batch Numbers:** The test product was rhIGF-IIIGFBP-3, Lot number DP9601. The study drug was administered by continuous subcutaneous infusion for seven consecutive days at 0.5, 1.0, or 2.0 mg/kg/day.

**Duration of Treatment:** Seven consecutive days at 0.5, 1.0, or 2.0 mg/kg/day.

**Reference Therapy, Dose and Mode of Administration, Batch Number:** The placebo product was the same buffer solution used for the formulation of the study drug, i.e. 50 mM sodium acetate, 105 mM sodium chloride, pH 5.5, lot number DP9602.

## CRITERIA FOR EVALUATION

Pharmacokinetics: Serum concentrations of I(1W-I and IGFBP-3 were determined, and non-compartmental pharmacokinetic parameters C<sub>max</sub>, T<sub>max</sub> and AUC(0-168) were evaluated for

each compound at different dose levels. In addition, a one-compartment open-model with constant infusion was used for the determination of C<sub>ss</sub> at different dose levels.

**Pharmacodynamics:** Serum concentrations of bone alkaline phosphatase, osteocalcin and collagen, and ratios of urine N-telopeptides to creatine and urine deoxypyridinolines to creatine were measured at different dose levels of IGF-I and IGFBP-3. All the concentrations and concentration ratios were compared to each subject's baseline concentrations.

**Safety:** Safety parameters included physical examination, ECG and clinical laboratory tests. Vital signs and adverse events were monitored during the course of the study.

**Statistical Methods:**

**Pharmacokinetics:** Descriptive statistics were calculated for IGF-I and IGFBP-3 concentration data and pharmacokinetic parameters. Dose proportionality was evaluated by dose normalizing the baseline adjusted pharmacokinetic parameters of IGF-I and IGFBP-3 to give plots of dose versus AUC(0-168)/Dose, C<sub>max</sub>/Dose and C<sub>ss</sub>/Dose.

**Pharmacodynamics:** Descriptive statistics (i.e., number of observations, mean, minimum, maximum, coefficient of variation, standard deviation, and standard error of mean) were provided for all variables by treatment.

**Safety:** Descriptive statistics were used to summarize safety parameters.

**SUMMARY-**

**Pharmacokinetic results:** Summary pharmacokinetic parameters at different dose levels are presented in the following table for IGF-I and IGFBP-3, respectively.

Arithmetic Mean (SD) Pharmacokinetic Parameters for IGF-I					Arithmetic Mean (SD) Pharmacokinetic Parameters for IGFBP-3				
Dose	0mg/kg Placebo	0.5mg/kg	1.0mg/kg	2.0mg/kg	Dose	0mg/kg (Placebo)	0.5mg/kg	1.0mg/kg	2.0mg/kg
C <sub>max</sub> (ng/mL)	19.33 (14.74)	303.3 (137.5)	652.0 (101.6)	893.3 (233.9)	C <sub>max</sub> (µg/mL)	0.4667 (0.0577)	1.100 (0.3606)	2.233 (0.7506)	2.300 (0.7937)
T <sub>max</sub> (hr)	24.5 (41.1)	104 (55.4)	72.0 (41.6)	64.0 (13.9)	T <sub>max</sub> (hr)	96.3 (86.0)	88.0 (73.3)	88.0 (36.7)	64.0 (13.9)
AUC(0-168) (ng*hr/mL)	968.0 (890.9)	36740 (13550)	80260 (6971)	101300 (34560)	AUC(0-168) (µg*hr/mL)	26.33 (13.08)	100.2 (36.79)	247.7 (68.13)	248.9 (118.7)
C <sub>b</sub> (ng/mL)	128.3 (52.69)	98.00 (16.52)	147.0 (54.67)	92.67 (31.26)	C <sub>b</sub> (µg/mL)	2.667 (0.4163)	2.467 (0.4933)	2.933 (0.4041)	2.733 (0.5033)
*C <sub>ss</sub> (ng/mL)	--	271.4 (123.8)	583.0 (100.3)	654.5 (243.9)	*C <sub>ss</sub> (µg/mL)	--	0.6981 (0.3800)	1.684 (0.5932)	1.553 (0.7465)
**C <sub>ss</sub> (ng/mL)	--	369.4 (135.6)	730.0 (101.8)	747.2 (251.5)	**C <sub>ss</sub> (µg/mL)	--	3.165 (0.7473)	4.617 (0.6668)	4.287 (1.007)

\*C<sub>ss</sub> (ng/mL) - baseline adjusted steady-state concentration, calculated by one compartment open model with constant infusion.

\*\*C<sub>ss</sub> (ng/mL) - non-baseline adjusted steady-state concentration (C<sub>ss</sub> = C<sub>ss</sub> + C<sub>b</sub>).

**PHARMACODYNAMICS:** In general, serum concentrations of bone alkaline phosphatase, osteocalcin and collagen, and urine concentration ratios of N-telopeptides to creatine and deoxypyridinolines to creatine showed some degree of increase in groups receiving rhIOF-1/IOFBP-3 compared with the placebo group. The concentration-time curves of each of these endocrine and bone metabolism markers at three different doses were above the placebo curve during the administration period, indicating an increase of endocrine and bone metabolism markers due to the administration of the drug. However, all of the values showed considerable fluctuation.

**SAFETY:** During the trial there were a total of 65 treatment-emergent adverse events reported by 12 of the 12 subjects enrolled in the trial. The majority of the events were mild in severity and resolved without treatment. No serious adverse events were reported during the study. Injection site hypersensitivity (verbatim terms "erythema" and "pruritus" at injection site) and headache were the most common treatment-related adverse events reported during the trial, occurring overall following the active treatment. No clinically significant trends in vital signs, physical examinations, ECGs or clinical laboratory tests were observed regarding subject safety with respect to the different treatment regimens. Erythema at the injection site was noted on eight of the nine subjects following the active treatment.

**Sponsor's conclusion:**

The pharmacokinetics and safety of rhIGF-J and rhIGFBP-3 were investigated in healthy elderly female subjects following the continuous subcutaneous infusion of rhIOF-1/IGFBP-3 for seven days. The study drug appeared to be safe and generally well-tolerated by the study subjects, with erythema and pruritus at the injection site being the most common adverse event reported.

This was a randomized, double-blind, placebo-controlled sequential cohort dose escalation study, with 0.5, 1.0 and 2.0 mg/kg/day dose levels investigated. Although each dose was administered at a continuous rate, there were considerable fluctuations in mean concentration values with time, particularly for IGFBP-3. Overall, the 1.0 mg/kg/day dose appeared to give the most stable blood levels of both IGF-I and IGFBP-3, while the 2.0 mg/kg/day dose level resulted in the least stable concentrations.

The relationship between dose and the pharmacokinetic parameters  $C_{max}$ ,  $C_{ss}$  and  $AUC(0-168)$  was not linear within the range of the administered doses, although it is not statistically significant. The administration of the highest dose resulted in lower than expected  $C_{max}$ ,  $C_{ss}$  and  $AUC(0-168)$ , indicating increased clearance rate probably caused by saturation of some pharmacological process involved in maintaining serum levels of IGF-I and IGFBP-3.

Mean values of endocrine and bone metabolism markers showed some increases in subjects receiving rhIGF-/rhIGFBP-3. The concentration-time curves of each endocrine and bone metabolism marker at three different doses were above the placebo curve during the administration period, indicating an increase of endocrine and bone metabolism markers due to the administration of the drug. However, all of the values showed considerable fluctuation.

**Study INSM-110-601**

**Study Title:** A Phase I, Single Dose, Randomized, Cross-Over Study in Healthy, Adult Volunteers, Comparing the Safety, Tolerability and Pharmacokinetic Profiles of Subcutaneous Administration of recombinant human Insulin-Like Growth Factor-I / recombinant human Insulin-Like Growth Factor Binding Protein-3 (rhIGF-I/rhIGFBP-3) Manufactured at Two Different Manufacturing Facilities

**Protocol No.:** INSM-110-601

**Report Name:** INSM-110-601 Interim Clinical Study Report on IGF-I Pharmacokinetic Analysis for Bioequivalency (Document No. 05-0029)

**Name of Drug:** Recombinant human insulin-like growth factor-I/recombinant human insulin-like growth factor binding protein-3 (rhIGF-I/rhIGFBP-3).

**Name of Sponsor:** Insmmed Incorporated  
4851 Lake Brook Drive  
Glen Allen, VA 23060

**Development Phase:** Phase I

**Study Initiation:** July 24, 2005

**Study Completion Date:** August 16, 2005

**Coordinating Investigators  
And Institutions:**



**Sponsor Signatory:** Ronald D. Gunn, M.S., M.B.A.  
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**Number of Pages:** 15 plus Attachments, including Appendices 14.2.1, 14.2.2, 16.2.4.1, 16.2.6.1 and 16.2.6.2. (All other Appendices listed in the Statistical Analysis Plan will be included in the final report).

**Date of Interim Report:** 18 August 2005

**GCP Compliance****Statement:**

This study was designed and performed according to the principles in the Declaration of Helsinki and the Guidelines for Good Clinical Practice.

**Study Objective:**

The study objective is to compare the pharmacokinetic profiles and bioequivalence of subcutaneous administration of 0.5 mg/kg rhIGF-I/rhIGFBP-3 manufactured at Insmmed Therapeutic Proteins, Boulder CO, USA, (test material) relative to 0.5 mg/kg rhIGF-I/rhIGFBP-3 manufactured at Avecia, Billingham, UK, (reference material) in adult, healthy male and female volunteers.

**Study Design:**

This study was a single-dose, randomized, open-label, two-period crossover, bioequivalence study of rhIGF-I/rhIGFBP-3 manufactured at two different manufacturing facilities. Avecia drug product was used as the reference drug product to compare with Insmmed Therapeutic Proteins drug product.

Up to 30 healthy male and female subjects were to be enrolled in the study, with the expected completion of at least 24 subjects. Each subject was randomized to receive a single dose (0.5 mg/kg) of Avecia drug product or ITP drug product during each of the study periods, such that, by the end of the study, each subject had been treated with both drug products in random order. Blood samples for determination of IGF-I, IGF-II, IGFBP-3, and acid labile subunit (ALS) concentrations were obtained prior to dosing (0 hour) and at specified times over 72 hours following the dosing. Subjects were confined to the clinical research facility from the evening prior to dosing through the 72-hour post-dose procedures. A minimum 7-day washout period occurred between study periods.

Safety was assessed throughout the study by evaluating adverse events, blood chemistries including glucose concentrations, hematologies, urinalyses, physical examinations, vital signs and electrocardiograms. A schedule of study procedures can be found in the protocol in Attachment 6.

This interim report provides pharmacokinetic data for IGF-I in order to report the results for the primary endpoint of drug bioequivalence. Safety assessments and other protein/peptide data will be described in the final report.

**INVESTIGATIONAL DRUG PRODUCT:**

Drug products manufactured at two different facilities were used in the study:

- Commercial-scale drug product test material manufactured at Insmmed Therapeutic Proteins in Boulder, CO, USA., hereafter referred to as ITP drug product (Lot # DP0503); and
- Commercial-scale drug product reference material manufactured at Avecia in Billingham, UK, hereafter referred to as Avecia drug product (Lot # DP0404).

rhIGF-I/rhIGFBP-3 manufactured at Avecia and at ITP was prepared as a 60 mg/mL premixed solution. The formulation contains 50 mM sodium acetate and 105 mM sodium chloride, pH 5.5. The complex is — under GMP conditions and released per Inmed specifications.

## DRUG Concentrations and Pharmacokinetic parameters

### Methods for Drug Concentration Measurements

Total IGF-I was assayed using the — ELISA Kit which was used according to Inmed SOP — All of the manufacturer's procedures were followed as specified in the written method for this ELISA.<sup>2</sup> For the purpose of this assay, the limit of quantitation was defined as the lowest standard provided with the kit used to generate the standard curve. Typically, the lowest standard was — ng/mL. Sample values were calculated based on the standard curve generated from the provided standards.

### Pharmacokinetic Parameters

Serum samples were collected pre-dose and then at specific post-dose time points for a 72-hour time period to measure serum levels of IGF-I. Primary and secondary pharmacokinetic parameters (as defined in the Statistical Analysis Plan, Attachment 7) have been determined for IGF-I for both Avecia and ITP drug product.

#### Primary Pharmacokinetic Parameter:

$AUC_{0-T_{last}}$  Area under the serum concentration curve from time 0 to last measurement

#### Secondary Pharmacokinetic Parameters:

$AUC_{0-\infty}$  Area under the serum concentration time curve from time of dosing to infinity

$C_{max}$  Maximum serum concentration over the entire sampling period

$T_{max}$  Time to attain  $C_{max}$

$k_{el}$  Apparent elimination rate constant

$t_{1/2}$  Apparent elimination half-life

## Statistical Methods for Analysis of Pharmacokinetic Parameters

### *Statistical Methods*

The last scheduled sample in each study period was at 72 hours, therefore  $AUC_{0-T_{last}}$  is  $AUC_{0-72}$ .  $AUC_{0-T_{last}}$  was calculated using the linear trapezoidal rule. Using an unweighted regression analysis,  $k_{el}$  was estimated using all post-24-hour concentrations in profiles in which  $T_{max}$  was less than or equal to 24 hours; otherwise,  $k_{el}$  was estimated using all concentrations from  $T_{max}$  through 72 hours.  $AUC_{0-\infty}$  was estimated by extrapolating  $AUC_{0-T_{last}}$  to baseline using the following equation  $AUC_{0-\infty} = AUC_{0-T_{last}} + C_{T_{last}} / k_{el}$ . Half-life was calculated using  $\ln(2) / k_{el}$ .

Pharmacokinetic parameters were summarized separately using baseline-corrected or uncorrected data. The baseline-corrected values were formed by subtracting the pre-injection concentration of IGF-I (nominal time zero) from each post-injection concentration for that individual and that treatment period.

### *Considerations Unique to rhIGF-I/rhIGFBP-3*

The pharmacokinetics of IGF-I following subcutaneous injection of rhIGF-I/rhIGFBP-3 are complex, which complicates the calculation of  $k_{el}$ ,  $t_{1/2}$ , and  $AUC_{0-\infty}$ ; the calculation of baseline-

corrected parameters; and the ultimate assessment of bioequivalence. Confounding factors include:

- Endogenous and exogenous IGF-I cannot be distinguished in the assay. Healthy adults have substantial concentrations of endogenous IGF-I that are variable between subjects and can vary somewhat within a subject. Thus, differences in baseline concentrations from one study period to the next for the same subject may reflect baseline variability rather than a true change in baseline value. This variability adds noise to the dataset when applying baseline correction.
- Endogenous circulating IGF-I is present primarily as part of a ternary complex bound to IGFBP-3 and ALS, which reportedly prolongs the effective half-life of IGF-I from approximately 15 minutes to 12-20 hours.<sup>3,4</sup> Exogenously administered rhIGF-I/rhIGFBP-3 likely combines with excess circulating endogenous ALS, to form the ternary complex.<sup>5</sup> Baseline ALS levels may affect the pharmacokinetics of rhIGF-I/rhIGFBP-3 (particularly in patients with conditions causing ALS deficiency, such as growth hormone (GH) deficiency or resistance).
- IGFBP-3 in the circulation is normally saturated and is not in excess, and it is bound to either IGF-I or IGF-II creating an equimolar environment where IGFBP-3 equals the sum of IGF-I and IGF-II.<sup>6</sup> Administration of exogenous IGF-I in complex with IGFBP-3 may acutely alter basal endogenous IGF-I levels, in that a change in any of these three components will affect the other two. Exogenous IGF-I administration typically causes a transient reduction in IGF-II, as well as feedback inhibition of pituitary GH production and secretion, which is the primary, positive regulator of IGFBP-3 and ALS production.<sup>7</sup> As such, dynamic changes in the levels of endogenous IGF-I, IGF-II, IGFBP-3 and ALS may affect the apparent pharmacokinetics of IGF-I.
- The decline of blood levels of IGF-I observed after  $C_{max}$  is attained may not follow a first-order, log-linear pattern, due to the complexities of the binding proteins and IGF-I elimination. Thus, it is not known if the slope of the elimination phase is constant after the 72-hour sample and extrapolation may not accurately represent the actual values. For this reason, the truncated  $AUC_{0-Tlast}$ , which does not require extrapolation, is the preferred primary pharmacokinetic parameter.

#### *Bioequivalence Testing Method*

The bioequivalence analysis consists of assessing whether the 90% confidence interval for the ratio of test-to-reference formulation means (ITP drug product to Avecia drug product) lies within the limits (0.80, 1.25). Per the Statistical Analysis Plan, the primary assessment of bioequivalence is performed using baseline-corrected IGF-I  $AUC_{0-Tlast}$ .

$AUC_{0-Tlast}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$  are assumed to be log-normally distributed. The testing method for log-normally distributed data is the following: (1) Pharmacokinetic outcomes are log-transformed for each study participant and the analysis is performed on a logarithmic scale, (2) the 90% confidence interval is calculated for the difference between the test and reference means on the log-transformed scale, (3) the endpoints of the 90% confidence interval are exponentiated to return to the original scale of measurement, and (4) if the 90% confidence interval lies between (0.80, 1.25), bioequivalence is concluded. The 90% confidence intervals for  $T_{max}$ ,  $k_{el}$  and  $t_{1/2}$  were constructed by approximating the standard error for the estimated ratio via the delta method.<sup>8</sup>

All pharmacokinetic statistical analyses were conducted using SAS software version 9.1.

### Data Quality Assurance

For this interim report on IGF-I pharmacokinetic parameters of ITP and Avecia drug products, the investigational site was monitored and case report forms were collected. CRFs were reviewed by the Clinical and Data Management Departments at Inmed Incorporated. Data entry of IGF-I concentrations and demographic data were 100% verified. The study database continues to be updated with safety and laboratory data and as such is not locked as of this report.

### Study Subjects

#### Disposition of Subjects and Study Populations

Thirty subjects were enrolled in the study and had at least one post-baseline safety assessment. These subjects comprise the safety population and will be discussed in the final report. Two subjects completed the first Study Period and were unable to return to the study site for the second Study Period due to logistical reasons, and were therefore withdrawn from the study (Subjects #001 and 011).

For one subject (assigned ID #002), the syringe malfunctioned during Study Period 1 dosing and the subject received an unknown amount of drug. Study Period 1 procedures were not performed. She was re-enrolled (as subject #020) at a later date and successfully completed both Study Periods.

Twenty-eight subjects received doses of both ITP and Avecia study drug product, and completed all study procedures, including adequate blood sampling for pharmacokinetic parameter determination. These 28 subjects were included in the Evaluable Population for IGF-I pharmacokinetic analysis and are described in this report.

#### Demographic and Baseline Characteristics

Table 1 displays the demographic and baseline characteristics for subjects included in the pharmacokinetic analysis (Attachment 2 contains an individual subject listing for demographics and baseline characteristics). Table 1. Demographic and Baseline Characteristics

Variable	Evaluable Population (n=28)
Sex (n, %)	
Male	24 (86%)
Female	4 (14%)
Race (n, %)	
White	7 (25%)
Black	17 (61%)
Asian	2 (7%)
Other	2 (7%)
Age (yr)	
Mean $\pm$ SD	36 $\pm$ 8.1
Median	35.8
Range	21.0 – 48.9

Variable	Evaluable Population (n=28)
Weight (kg)	
Mean ± SD	76.4 ± 12.6
Median	74.0
Range	55.0 – 98.5
Height (cm)	
Mean ± SD	173.5 ± 8.1
Median	173.0
Range	160.0 – 185.0

#### BIOEQUIVALENCY AND Pharmacokinetic Results

Table 2 presents the pharmacokinetic parameters used for determining bioequivalence. Baseline corrected and uncorrected means, standard deviations, drug product ratios, and confidence limits are included. Figures 1 and 2 show baseline-corrected and uncorrected mean IGF-I concentrations, respectively, after administration of 0.5 mg/kg Avecia drug product and 0.5 mg/kg ITP drug product.

#### *Primary Bioequivalence Analysis*

Average bioequivalence was demonstrated for the primary outcome variable (as defined in the Statistical Analysis Plan), the baseline-corrected  $AUC_{0-Tlast}$ , where the 90% confidence interval is (1.11, 1.25) and is contained within (0.80, 1.25). The data are shown in Table 2 and Figure 1.

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*Secondary Pharmacokinetic Analysis*

The confidence intervals for baseline-corrected  $AUC_{0-\infty}$  and  $C_{max}$  did not lie within (0.80, 1.25). For the reasons stated in the Section 6.3 (*Considerations Unique to rhIGF-I/rhIGFBP-3*), the assessment of these pharmacokinetic parameters may be better evaluated without correcting for the baseline concentrations, as this approach requires the fewest assumptions and reduces the additional error introduced by the variation of basal endogenous IGF-I levels.

In analyses conducted using uncorrected IGF-I data,  $AUC_{0-Tlast}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$  all satisfy the requirements of average bioequivalence. The data are shown in Table 2 and Figure 2.

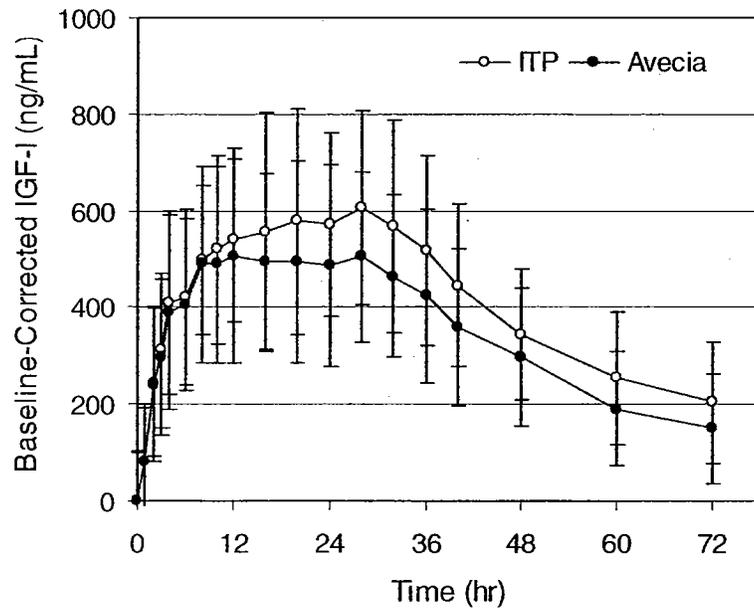
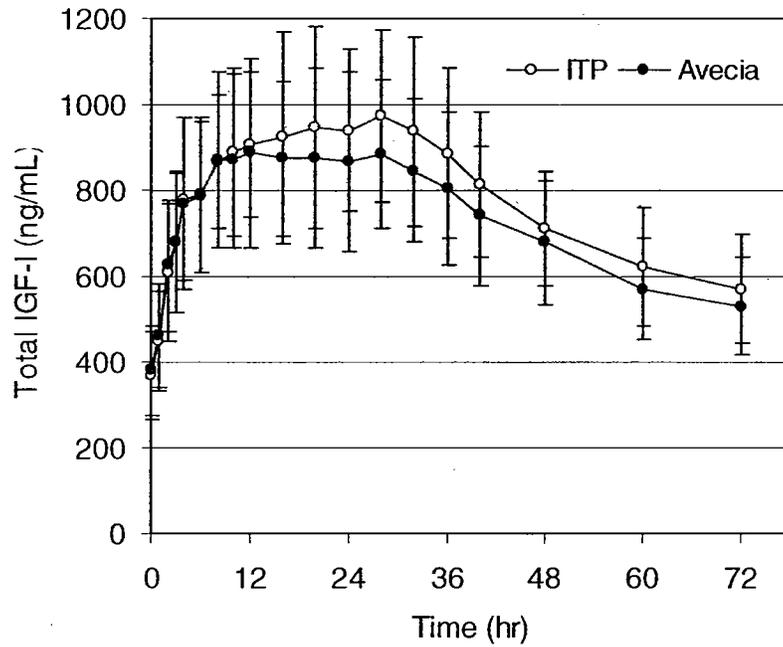
**Table 2. IGF-I Pharmacokinetic Parameters for Bioequivalence After Administration of a Single Dose of Avecia Drug Product and ITP Drug Product (N=28)**

IGF-I PK Parameters	Baseline Corrected		Uncorrected	
	Avecia Drug	ITP Drug	Avecia Drug	ITP Drug
$AUC_{0-Tlast}$ (ng/ml*hr)				
Mean ± SD	25262 ± 6514.7	29684 ± 6850.4	52682 ± 10066.1	56184 ± 10350.2
Geometric Mean	24493	28908	51593	55134
Avecia/ITP Ratio	1.18		1.07	
CI	1.11 – 1.25		1.04 – 1.09	
$AUC_{0-\infty}$ (ng/ml*hr)				
Mean ± SD	31536 ± 8083.4	38049 ± 8951.0	103606 ± 43461.4	105875 ± 31764.9
Geometric Mean	30480	36950	97851	101733
Avecia/ITP Ratio	1.21		1.04	
CI	1.11 – 1.33		0.98 – 1.10	
$C_{max}$ (ng/ml)				
Mean ± SD	594 ± 172.8	721 ± 209.5	974 ± 206.3	1089 ± 251.1
Geometric Mean	573	698	951	1065
Avecia/ITP Ratio	1.22		1.12	
CI	1.13 – 1.31		1.06 – 1.18	

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**Figure 1. Comparison of Mean ( $\pm$  SD) Baseline-Corrected IGF-I Serum Concentrations After Administration of Avecia and ITP Drug Products**

**Figure 2. Comparison of Mean ( $\pm$  SD) Uncorrected IGF-I Serum Concentrations After Administration of Avecia and ITP Drug Products**



The mean time to peak IGF-I concentration was similar for Avecia drug product and ITP drug product ( $T_{max}$  of 19.5 hours for Avecia and 21.6 hours for ITP). The mean half-life calculated using baseline-corrected concentrations was also similar for Avecia and ITP drug products,  $26.2 \pm 11.80$  hours and  $27.6 \pm 6.95$  hours, respectively. The elimination rate constant was  $0.034 \text{ hr}^{-1}$  for Avecia drug product and  $0.027 \text{ hr}^{-1}$  for ITP drug product.

***Reviewer's comments:***

This BE study was conducted in healthy subjects, who had normal IGF-1 levels comprising of about 50% of the total exposure and early exposure. With such substantial contribution of baseline in IGF-1, it is rational using baseline corrected PK parameters to do BE analysis. Apparently,  $C_{max}$  is off the 90% confidence interval though AUC (0-last) barely passed the criteria with upper limit of 125 from baseline corrected BE analysis. From point estimates, the new drug products manufactured in Boulder, Colorado may produce 18% and 22% more in AUC and  $C_{max}$ , respectively. Therefore, the sponsor failed to establish bioequivalence between new drug products and the reference drug products used in Cohort #2.

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/s/

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Xiao-xiong Wei  
9/14/2005 11:23:18 AM  
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Individual study review for NDA21-884

Hae-Young Ahn  
9/14/2005 04:18:40 PM  
BIOPHARMACEUTICS

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

**General Information About the Submission**

<b>NDA Number</b>	21-884	<b>Brand Name</b>	Mecasermin rinfabate
<b>OCPB Division (I, II, III)</b>	DPE II	<b>Generic Name</b>	rhIGF-1/rhIGFBP-3
<b>Medical Division</b>	HFD-510	<b>Drug Class</b>	Growth hormone
<b>OCPB Reviewer</b>	Xiaoxiong (Jim) Wei	<b>Indication(s)</b>	Growth hormone insensitivity syndrome
<b>OCPB Team Leader</b>	Hae-Young Ahn	<b>Dosage Form</b>	60 mg/mL
		<b>Dosing Regimen</b>	1 – 2 mg/kg daily
<b>Date of Submission</b>	12-31-04	<b>Route of Administration</b>	Subcutaneous injection
<b>Estimated Due Date of OCPB Review</b>	05-20-05	<b>Sponsor</b>	Insmed, Inc.
<b>PDUFA Due Date</b>	06-31-05	<b>Priority Classification</b>	P1
<b>Division Due Date</b>	05-31-05		

**Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
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			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	1		
multiple dose:	X	2		
<i>Patients-</i>				
single dose:	X	2		
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:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		5		
<b>Filability and QBR comments</b>				
	<b>"X" if yes</b>	<b>Comments</b>		
<b>Application fileable?</b>	YES			
<b>Comments sent to firm?</b>	NO			

**Briefing in Content:**

The drug product is a binary protein complex of recombinant human insulin-like growth factor I (rhIGF-I) and recombinant human insulin-like growth factor-binding protein-3 (rhIGFBP-3) for subcutaneous injection and is indicated for the treatment of childrens with growth failure due to severe growth hormone insensitivity syndrome (hereditary or acquired) resulting in IGF-I deficiency and presenting with height standard deviation score less than or equal to -3 and IGF-I SDS less than or equal to -

The sponsor submitted 5 PK studies including one single dose PK study in healthy subjects, one multiple dose PK study in healthy subjects, one continuous subcutaneous infusion PK in healthy subjects, two single dose studies in patients with GHIS.

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Hae-Young Ahn  
3/16/05 05:42:56 PM  
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