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**APPLICATION NUMBER**

**NDA 21-839**

**Clinical Pharmacology and Biopharmaceutics  
Review**

## ADDENDUM

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NDA: 21-839  
Submission Date: February 24, 2005 / August 18, 2005 / August 23, 2005  
Reviewer: Sang M. Chung, Ph.D.  
Team Leader: Hae-Young Ahn, Ph.D.

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The bioequivalence for the Study F0580g was assessed using the pharmacokinetic parameters estimated with IGF-1 plasma concentrations after the baseline adjustment. Results of statistical analysis were summarized in the following table, and the results met the bioequivalence criteria.

**Table Bioequivalence Parameters for Total IGF-1 (Adjusted for Baseline IGF-1 Concentration) After SC Bolus Administration of Mecasermin in Healthy Subjects (F0580g)**

Computed Parameter <sup>b</sup>	Means <sup>a</sup>			Classical t-test 90% confidence limits
	I	J	Ratio of Geometric Means $\frac{\bar{I}}{\bar{J}}$ [100]	
Log <sub>10</sub> AUC(0-72hr)	5.63	5.62	101.6	95.2-108.3
Log <sub>10</sub> Cmax	2.41	2.40	102.2	96.0-108.7

<sup>a</sup> Least squares means

<sup>b</sup> Noncompartmental pharmacokinetic analysis

N=32, 31 of the 32 subjects were common to both treatments

Dose = 0.08 mg/kg SC

Composite male/female data

Data were corrected for endogenous total IGF-1 concentrations:

Baseline = average of IGF-1 levels at 5 and 15 minutes predose

Baseline adjusted IGF-1 levels = (postdose IGF-1 levels) – (the baseline)

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Sang Chung  
8/25/2005 02:31:32 PM  
BIOPHARMACEUTICS

Hae-Young Ahn  
8/26/2005 04:56:25 PM  
BIOPHARMACEUTICS

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
REVIEW**

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NDA: 21-839  
Submission Date(s): February 24, 2005  
Brand Name: Increlex  
Generic Name: Mecasermin [rDNA origin] injection  
Reviewer: Sang M. Chung, Ph.D.  
Team Leader: Hae-Young Ahn, Ph.D.  
OCPB Division: DPE 2  
ORM division: DMEDP  
Sponsor: Tercica Medica  
Relevant IND(s): IND — IND IND 39679  
Submission Type: Original NDA  
Formulation: 10mg/ml sterile solution in 5 ml multiple dose glass vials  
Indication: Long-term treatment of growth failure in children with primary IGF-1 deficiency

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## 2 Executive Summary

### 2.1 Recommendation

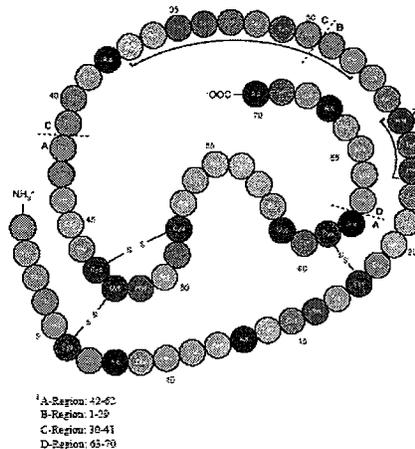
The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation 2 (OCPB/DPE2) has reviewed NDA 21-839 and finds it acceptable. The Recommendation should be sent to the sponsor as appropriate.

### 2.2 Phase IV Commitments

None

### 2.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Increlex™ (mecasermin [rDNA] injection) is a non-glycosylated human insulin like growth factor-1 (hIGF-1) produced by recombinant DNA technology (rDNA). IGF-1 is a hormone structurally related to human insulin. It has 70 amino acids (M.W.=7649 daltons), and amino acid sequence of the product is identical to that of endogenous human IGF-1 (Figure 1).



**Figure 1** Amino acid sequence of rhIGF-1; disulfide bridges (-s s-), receptor binding domains (-), and sequence regions (...)

IGF-1 is produced in the body as the response to growth hormone (GH), and then induces subsequent tissue responses, particularly in stimulating bone growth. In addition to mediating activities of GH, it also has insulin-like metabolic activities. It is indicated for growth failure in children with primary IGF-1 deficiency (IGFD). Primary IGFD is from defects in GH action despite normal blood GH levels. The proposed indication is designated as an orphan indication.

The proposed target population is children who with height standard deviation (SD) score is less than or equal to -3.0 and with basal IGF-1 SD score is less than or equal to -3.0, in the presence of normal or elevated GH. The recommended starting dose is 0.080 mg/kg BID by SC injection shortly before or after a meal or snack. The dose may be increased to 0.120 mg/kg. Injection sites should be rotated to a different site with each injection. The proposed dosing regimen is to maintain blood IGF-1 levels in or near the normal range.

Total 9 reports of CPB studies were included in this NDA for CPB review. Clearance in patients was higher than that in healthy subjects. Mean clearance of total IGF-1 was 0.0424 L/h/kg after SC injection of mecasermin in patients with severe IGFD, and half-life after 0.12 mg/kg was 5.8 hr (n=3).

IGF binding protein (IGFBP-3) in blood accounts for more than 80% binding proteins for mecasermin, and the clearance of mecasermin is inversely proportional to levels of IGFBP-3. IGFBP-3 is significantly low in primary IGFD patients compared to that in normal subjects.

The absolute bioavailability after SC seemed to be close to 100% based on a cross study comparison. Renal excretion appeared to be a major clearance pathway after metabolism.

There was no specific study for special populations. It was difficult to estimate the effect of covariates on mecasermin pharmacokinetics due to small number of subjects studied with complicating factors including baseline IGF-1 levels, and IGFBP-3 levels though there was an attempt to address the issues using a population pharmacokinetic analysis.

Mecasermin used in clinical trials was made by [redacted] and those were named as the [redacted].

[redacted] Two bioequivalence (BE) studies were conducted to measure comparability of the different manufacturing processes. One study demonstrated bioequivalence between the [redacted] [redacted], and the other study met the BE criteria between [redacted] [redacted] processes. Mecasermin by [redacted] [redacted] process was used in most clinical studies, and the marketed product will be produced by the [redacted].

Radioimmunoassay (RIA) was used to measure total and free IGF-1.

### 3 Question-Based Review (QBR)

#### 3.1 General Attributes

3.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Genentech initiated development of mecasermin for children with short stature, and terminated the program in 1997. In 2002, the sponsor (Tercica) acquired Genentech's intellectual property rights with other information including non- and clinical data, and continued the development. Mecasermin clinical development programs were largely based on study results and protocols transferred from Genentech.  $\square$

Total of 9 CPB studies were conducted. Primary PK information by the proposed dosage regimen in the target population was characterized in the Study M302. Two BE studies were conducted to evaluate comparability of changes in manufacturing processes changes; Study F0580g (SC) and Study F0176g (IV bolus). Several other CPB studies were conducted using different routes of administration; SC (F0317g), IV bolus (F0115g, F0152g, F0188g) and IV infusion (F0174g, F0183g).

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

Mecasermin is recombinant human insulin-like growth factor-1 (rhIGF-1). The human IGF-1 consists of 70 amino acids with a molecular weight of 7649 Daltons. IGF-1 is highly homologous with human insulin as summarized in Figure 2. IGF-1 is produced by GH binding to the GH receptor mainly from the hepatic cells, bone and other tissues.

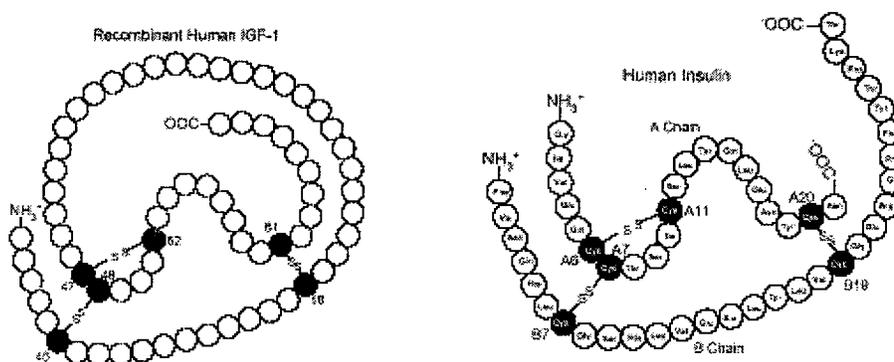


Figure 2 Comparison of rhIGF-1 (left) and human insulin (right)

Initially, Genentech developed a formulation (1989-1994) in a single-dose citrate buffer at pH6.0 for an intravenous delivery. Mecasermin was initially produced by  $\text{L}$  processes, and the formulation was used in early clinical safety studies. Genentech changed  $\text{L}$  to acetate mainly for multi-dose format and mecasermin was produced by  $\text{L}$  processes before termination of the program in 1997. Detailed summary on formulation is in Section 3.5 (General Biopharmaceutics).

### 3.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

IGF-1 is a hormone with autocrine and paracrine activities. It induces metabolic and tissue growth, particularly in cartilage and bone. It is indicated for growth failure in children with primary IGF-1 deficiency (IGFD) despite normal blood GH levels.

### 3.1.4 What are the proposed dosage(s) and route(s) of administration?

The recommended starting dose is 0.080 mg/kg BID by SC injection shortly before or after a meal or snack. The dose may be increased to 0.120 mg/kg.

## 3.2 General Clinical Pharmacology

### 3.2.1 What are the clinical endpoints or surrogate endpoints?

The primary efficacy endpoint was height velocity, and the secondary end point was height SD score. Mean height velocity increased from 2.8 cm/yr pre-treatment, to 8.0 cm/yr during the first year of treatment (n=58).

### 3.2.2 What are the major adverse events?

Hypoglycemia and tonsillar hypertrophy were the major adverse events. Tonsillar hypertrophy sometimes caused snoring and upper airway obstruction. Hypoglycemia was reported in 42% of patients (n=30), and 47% patients (n=14) with the adverse event had a hypoglycemia history before the treatment. Tonsillar hypertrophy was reported in 15% of patients (n=11).

### 3.2.3 What are the characteristics of exposure-response relationship?

There was no formal exposure-response characterization. Dose of 0.06mg/kg SC BID for one year (Study F0632g) was reported to have marginally effect in improving height. Major acute adverse effect was hypoglycemia. The proposed dosing (i.e., 0.08mg/kg and 0.12mg/kg SC BID) was based on maintaining blood IGF-1 in or near the normal range, and acceptable safety profile.

### 3.2.4 Does this drug prolong the QT or QTc interval?

The issue was not addressed in this NDA, and the effect of IGF-1 on QT prolongation is currently not known.

3.2.5 What are the PK characteristics of the drug and its major metabolite?

3.2.5.1 What are the single dose PK parameters, and how does the PK of the drug in healthy volunteers compare to that in patients?

Single dose pharmacokinetics was characterized in healthy subjects and patients (9 years to 25 years) in Study M302, and representative results were summarized in Figure 3 and Table 1.

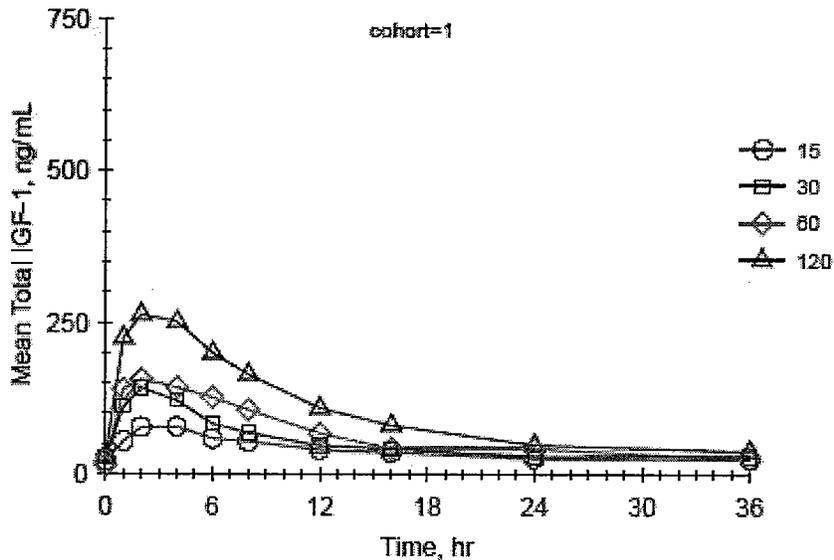


Figure 3 Mean total IGF-1 concentration – time profiles by dose in sever IGFD patients (concentration was adjusted by baseline).

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**Table 1 Mean and SD of mecaseimerin single dose pharmacokinetic parameters in healthy subjects and patients (sever IGFD and moderate IGFD).**

Parameter	Dose (mg/kg)	Severe IGFD (12 – 22 yrs)		Moderate IGFD (9-25 yrs)		Normal Healthy (11-25 yrs)	
		Mean	SD	Mean	SD	Mean	SD
C <sub>max</sub> (µg/mL)	0.015	0.059	0.005	0.094	0.023	0.104	0.011
	0.030	0.116	0.014	0.164	0.044	0.216	0.035
	0.060	0.170	0.030	0.201	0.026	0.238	0.027
	0.120	0.234	0.054	0.310	0.024	0.358	0.032
T <sub>max</sub> (hr)	0.015	2.67	1.15	14.00	11.14	4.67	3.06
	0.030	2.67	1.15	5.33	1.15	7.33	7.57
	0.060	3.33	2.31	2.67	1.15	14.67	18.58
	0.120	2.00	0.00	5.33	3.06	4.00	0.00
AUC(0-∞) (µg·min/mL)	0.015	43.0	15.0	264	182	187	62.3
	0.030	56.6	27.7	308	213	430	146
	0.060	125	66.7	260	158	615	273
	0.120	176	88.4	543	274	573	164
t <sub>1/2</sub> (hr)	0.015	9.4	2.3	25.0	19.7	12.6	5.5
	0.030	3.9	2.7	16.6	13.4	20.6	10.9
	0.060	9.7	3.5	13.6	5.3	26.2	24.2
	0.120	5.8	3.7	20.2	10.0	19.2	10.1

Noncompartmental analysis by WinNonlin version 3.2

- Baseline corrected IGF-1 concentrations were used in this analysis.
- n=3 per dose group in each category
- Source: MS302 Clinical Study Report

Clearance was higher in severe IGFD patients compared to that in healthy subject. IGF-1 clearance was inversely proportional to the levels of IGFBP-3, a major component for IGF-1 binding proteins, and IGFBP-3 levels were significantly lower in severe IGFD patients than those in normal subjects. Metabolites were not identified.

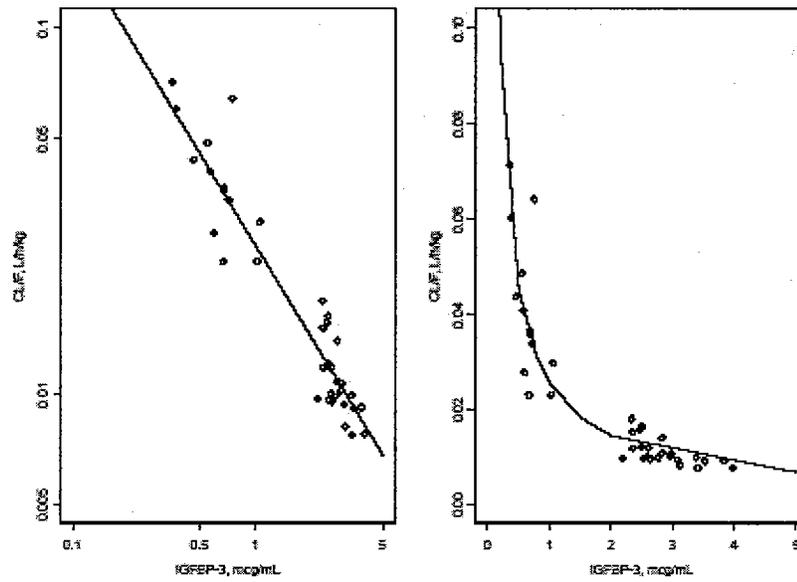
### 3.2.5.2 What are the characteristics of drug absorption?

The absorption rate constant after SC injection was  $0.93 \text{ hr}^{-1}$  from results of Study M302 using a population method with NONMEM. Time to reach maximum mecaseimerin plasma concentration was 2 hours after 0.12mg/kg SC injection in severe IGFD patients (Table 1).

Absolute bioavailability was estimated as close to be 100% based on a cross study comparison using AUCs. For example, the value was about 99% using mean of 269 min mcg/ml (n=22 healthy subjects) after 0.05mg/kg IV (Study F0176g ) and mean of 425.8 min mcg/ml (n=18 healthy subjects) after 0.08mg/kg SC (Study F0580g).

### 3.2.5.3 What are the characteristics of drug distribution?

Mecasermin was known to bind IGF binding protein (IGFBP) as a complex, and major binding proteins were IGFBP-3 and an acid-labile subunit. Clearance of IGF was known to be inversely proportional to levels of IGFBP-3 as shown in Figure 4



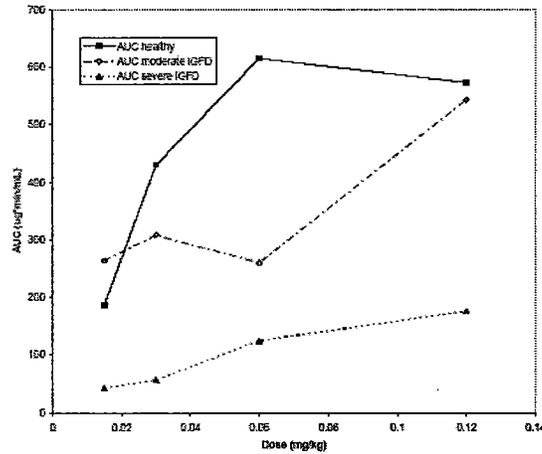
**Figure 4** Relationship between CL/F and IGFBP-3 concentrations. (left panel is for log-log scale, and right panel is for normal-normal scale)

### 3.2.5.4 What are the characteristics of drug elimination?

There was neither formal mass balance study nor metabolism study for mecasermin. Elimination half-life was 5.8 hours after 0.12 mg/kg SC injection in the patients.

### 3.2.5.5 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The sponsor concluded AUC was less proportional to the dose (Table 1, Figure 5). However, it should be noted that there were not enough numbers of subjects in each dose (3 subjects per dose).



**Figure 5** Mean total IGF-1 AUCs (n=3 in each group) for single SC in healthy subjects (closed square), moderate IGFD patients (open diamond), and severe IGFD patients (closed triangle).

3.2.5.6 How do the PK parameters change with time following chronic dosing? (This may include time to steady-state; single dose prediction of multiple dose PK; accumulation ratio.)

Mecasermin pharmacokinetics at steady-state was not estimated in the target population. Pharmacokinetic parameters at steady-state were simulated from those after single dose, and summarized in Table 2. Accumulation index (AI) was about 7.4 based on AUCs ratio.

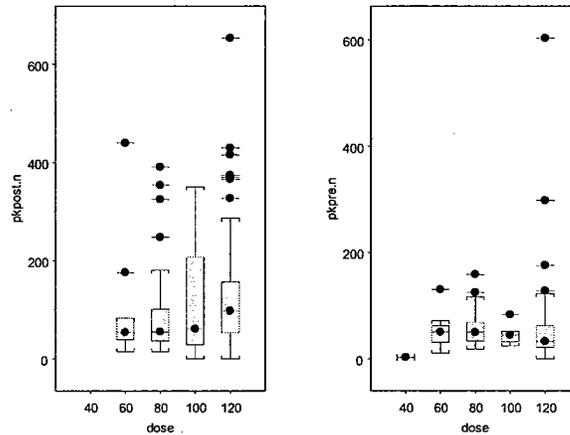
**Table 2** Summary of pharmacokinetic parameters after single dose, and simulated parameters at steady state in severe IGFD patients.

Dose (mg/kg)	Single Dose (MS302)				Multiple Dose Simulation	
	C <sub>max</sub> (µg/mL)	T <sub>max</sub> (hr)	AUC(0-∞) (µg·min/mL)	t <sub>1/2</sub> (hr)	C <sub>max</sub> (µg/mL)	AUC <sub>ss</sub> (0-12hr) (µg·min/mL)
0.015	0.059	2.67	43.0	9.4	0.0833	439
0.030	0.116	2.67	56.6	3.9	0.149	623
0.060	0.170	3.33	125	9.7	0.217	980
0.120	0.234	2.00	176	5.8	0.375	1659

Single dose data from study MS302 were analyzed using noncompartmental methods  
 N=12, 3 subjects per dose level, aged 12 to 22 yr  
 Male and female data combined, 3 male, 9 female  
 The single dose data in study MS302 and population PK model parameters developed from the single dose data were used to simulate the multiple dose data.  
 Data in study MS302 were corrected for endogenous total IGF-1 concentrations; data in the multiple dose simulation were not corrected for endogenous total IGF-1 concentrations  
 Source: MS302, Multiple Dose Simulation Report

However, AI appeared to be over-estimated based on results of the following indirect analyses.

IGF-1 concentrations were measured in safety/efficacy studies (Figure 6). Average (SD) of pre-dose IGF-1 concentrations ( $C_{trough}$ ) in the safety/efficacy studies was 51.7 (57.79) ng/ml, and it indicated that there was less than 2-fold accumulation compared to endogenous levels of IGF-1 in severe IGFD (29.3 (10.3) ng/ml, n=10 from Study M302).



**Figure 6** Total IGF-1 plasma concentrations at 2 hours post-dose (right panel; n=122ng/ml; 119.7±112.92) and at pre-dose (left panel; n=164; 51.7±57.79ng/ml) in safety/efficacy studies (Study F0375g, F0632g, F0671g, and 1419)

In addition, PK of mecasermin was estimated after multiple doses in healthy subjects (Table 3 and 4), and the results indicated accumulation was less than 1.6-fold by AUCs ratio. Clearance in patients is higher than that in healthy subjects, and thus accumulation is predicted to be less in patient than that in healthy subjects.

**Table 3** Mecasermin PK parameters after 0.1mg/kg SC BID in healthy male subjects.

Dose (mg/kg)	0.1	0.1	0.12	0.12
Sampling Time	SC BID 1 <sup>st</sup> dose	SC BID 4 <sup>th</sup> dose	SC BID 1 <sup>st</sup> dose	SC BID 4 <sup>th</sup> dose
C <sub>max</sub> (µg/mL)	0.437	0.652	0.377	0.696
T <sub>max</sub> (hr)	5.07	2.75	4.65	0.917
AUC(0-12hr) or (36-48hr) (µg·min/mL)	229	352	227	373
t <sub>1/2</sub> (hr)	21.1	33.6	29.6	32.5
V/F (mL/kg)	325	NC	474	NC
CL/F (mL/min/kg)	0.392	NC	0.310	NC

NC=not calculated

n=6 subjects per injection

CL/F and V/F estimated after subtraction of predose total IGF-1 concentrations; other parameters not corrected for endogenous concentrations

Noncompartmental PK analysis (WinNonlin Version 1.1)

Source: F0317g Part A

Table 4

Mecasermin PK parameters after 0.03mg/kg IV in healthy adult subjects.

Treatment Day	Day 1	Day 5
Parameter		
C <sub>max</sub> (ng/mL)	482 ± 102	525 ± 94
C <sub>pre</sub> (ng/mL)	120 ± 44	178 ± 62
C <sub>24</sub> (ng/mL)	166 ± 51	209 ± 89
AUC <sub>0-24</sub> (min·µg/mL)	269 ± 85	334 ± 105

- N=12
- Noncompartmental PK analysis
- The data was not corrected for endogenous levels.
- Study F0152g

3.2.5.7 What are the major causes of PK variability?

Clearance of mecasermin was inversely proportional to IGFBP-3 concentrations, and plasma concentration of IGFBP-3 was a factor for the PK difference between healthy subjects and patients. In addition, endogenous levels of IGF-1 changed with age (Figure 7), and it may be a confounding factor for intrinsic factor of mecasermin.

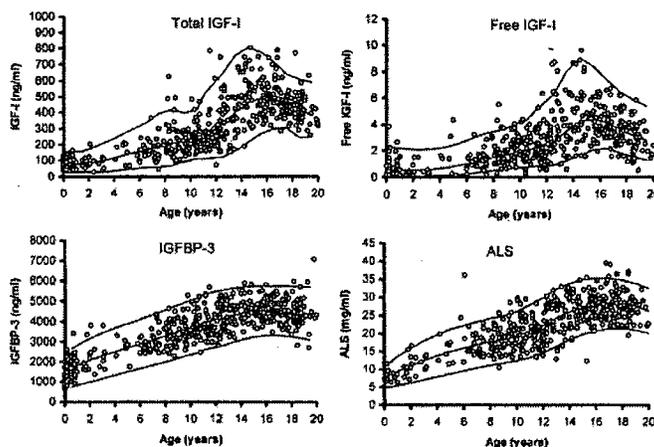


Figure 7 Levels of total IGF-1, free IGF-1, IGFBP-3, and ALS (acid-labile subunit) in healthy boys with age. Lines indicate mean and 2 SD. (Anders Juul, Growth Hormone & IGF Research 13 (2003):113-170)

3.2.5.8 Was there any population PK analysis?

A population PK model was developed to analyze the results of Study MS302 (Table 1), and PK parameters based on Bayesian method in NONMEM were summarized in Table 5.

**Table 5 Summary of PK parameters based on Bayesian method.**

Parameter*	Severe ICFD		Moderate ICFD		IGF-1 Normal	
	Mean	SD	Mean	SD	Mean	SD
$K_e$ ( $h^{-1}$ )	0.98	0.41	1.00	0.30	1.02	0.30
$K_{in}$ (mg/day)	0.67	0.12	2.17	0.66	4.09	0.81
( $\mu g/hr/kg$ )	0.94	0.10	1.82	0.23	2.82	0.27
Vd/F (L/kg)	0.257	0.073	0.259	0.067	0.259	0.066
CL/F (L/h/kg)	0.0424	0.0159	0.0132	0.0062	0.0107	0.0021

Note: Data represent a total of 12 subjects per IGF-1 cohort.

\* Based on individual PK parameters estimated by NONMEM compartmental analysis.

Source: MS302 Clinical Study Report

A one-compartment model with first-order absorption and elimination was employed to characterize IGF-1 pharmacokinetics. A zero-order input rate was used to describe the endogenous formation rate. Schematic summary of the model, population estimates and NONMEM control file were attached in Appendix.

### 3.3 What are the significant intrinsic or extrinsic factors for mecasermin pharmacokinetics?

There was no formal study to evaluate intrinsic (i.e., age, gender, and ethnicity) or extrinsic factors (i.e., drug interaction). Using cross study comparison, the sponsor concluded there were no apparent effects of age, gender, and ethnicity on mecasermin pharmacokinetics. However, numbers of subject were not sufficient enough to analyze all the covariates, and thus it should be cautious in the interpretation of results.

According to a reference provided by the sponsor, CL of IGF-1 in patients with chronic renal failure (n=6; mean creatinine clearance was 18 ml/min/1.73m<sup>2</sup>) was similar to that in healthy subjects after the single dose of 80mg/kg (appeared to be typo, and it should 80mcg/kg) SC injection (Table 6). However, Cmax was significantly higher in the renal patients than that in healthy subjects.

**Table 6 Mean (SD) PK parameters in chronic renal failure (CRF) patients and healthy subjects\***

	Total IGF-1		Free IGF-1	
	CRF	Normal	CRF	Normal
Cmax (ng/ml)	720 (180)	30 (63)	23 (3)	22 (7)
Vd (L/kg)	0.1 (0.22)	0.15 (0.05)	3.0 (0.6)	3.9 (2.0)
CL (ml/min/kg)	9.6 (4.7)	11 (5)	290 (160)	360 (180)

\* Insulin-like growth factor-I treatment to enhance renal function in advanced chronic renal failure, Fervenza *et al.* Renal Failure, 20:349-356 (1998)

### 3.4 General Biopharmaceutics

#### 3.4.1 Were there any significant manufacturing process changes and BE studies to evaluate comparability of changes?

There were two major process changes during the mecasermin development. The first change was [redacted]. The second change was from [redacted]. Majority of patient exposure in the clinical safety and efficacy study was from [redacted]. Two BE studies were conducted to measure comparability of the changes.

The BE study (Study F0176g) to measure comparability in the change from [redacted] [redacted] was conducted using a two-way crossover design in 24 healthy adult male subjects. Dose of 0.05 mg/kg was given to 10 seconds IV bolus in the forearm. BE assessment was conducted using PK parameters from free plasma IGF-1 concentrations. It was concluded that the study results met BE criteria with mean ratios (90% CI) of 1.02 (0.947-1.094) ng min/ml and 1.029 (0.918-1.141) ng/ml for  $AUC_{0-t}$  and  $C_{max}$ , respectively.

In addition, preliminary BE assessment was conducted using total IGF-1 data by this reviewer, and the results met the BE criteria. Mean ratios (95% CI) were 99.42 (94.4-104.7) and 107.98 (93.8-124.31) for AUC and  $C_{max}$ , respectively.

The second BE study (Study F0580g) evaluated comparability of the [redacted] [redacted] (G080AB, lot number A9809A2)/citrate-buffered (pH6.0) to [redacted] (G117AZ, lot number B9806A3)/acetate-buffered (pH5.4) in a phase I, two-period, crossover design in healthy men (n=19) and women (n=16). Age ranged from 18 years to 35 years. Dose of 0.08mg/kg was administered SC of arm. Plasma concentration-time profiles were shown in Figure 8. Pharmacokinetic parameters were calculated using the linear trapezoidal method, and results of BE assessment were summarized in Table 7. It was concluded that the results met BE criteria.

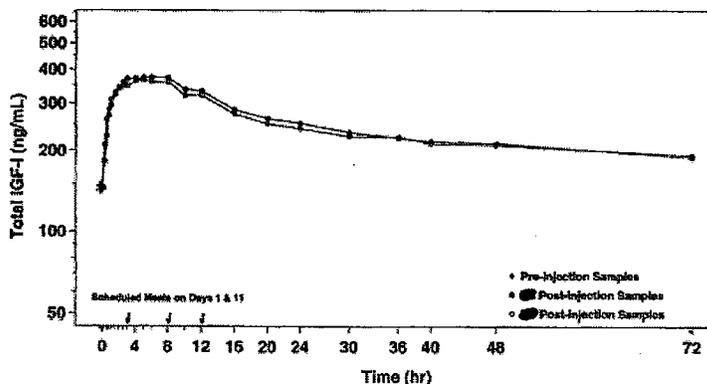


Figure 8 Mean total plasma IGF-1 concentration

Table 7 Results of BE assessment

Computed Parameter <sup>b</sup>	Formulation Means <sup>a</sup>		Ratio of Geometric Means — 100	Classical t-test 90% Conf. Limits
	acetate	citrate		
log <sub>10</sub> AUC <sub>0-72</sub>	6.02	6.01	102.1	98.1–106.3
log <sub>10</sub> C <sub>max</sub>	2.61	2.60	102.2	96.5–108.2

<sup>a</sup> Least squares means.

<sup>b</sup> Derived using noncompartmental techniques.

The to-be-marketed formulation will be manufactured by [ ] The sponsor claimed that the process change between [ ] were comparable based on physical/chemical and biological testing. The detailed changes were described in CMC documentation. There was teleconference (April 25, 2005) between the Agency (Attendee; Project manager, CMC reviewer, and OCPB reviewer) and the sponsor to clarify the sponsor's conclusion on the comparability, and it was concluded that the sponsor's claim was acceptable.

3.4.2 What were the components in the to-be-marketed formulation?

Components of the to-be-marketed formulation were summarized in Table 11.

Table 8 Summary of components in the to-be-marketed formulation

Component	Function	Quantity per mL	Quantity per Vial	Reference to Quality Standard
rhIGF-1	Drug Substance	10.0 mg	— g	In-house Specification
Sodium Chloride	—	5.84 mg	— g	USP/Ph. Eur.
Acetate,	—	—	— g	USP/Ph. Eur.
Polysorbate 20	—	2.0 mg	— g	USP/NF/Ph. Eur.
Benzyl Alcohol	Preservative	9.0 mg	— g	NF/Ph. Eur.
[ ]				[ ]

### 3.5 Analytical

#### 3.5.1 Was bioanalytical method acceptable?

A radioimmunoassay (RIA) method was used to measure plasma IGF-1 concentrations in the clinical studies. Genentech Test Procedure [ ] was used the majority of studies to measure total and free mecasemin plasma concentrations, and validation results were summarized in Table 12. The results were acceptable.

Table 9 Summary of assay validation

Reference	Qualification Summary
Assay Type	RIA
Calibration Curve Fit	[ ]
Sample Preparation	[ ] <sup>1</sup>
Sample Preparation Methods	[ ]
Quality Controls	[ ] <sup>1</sup>
Standard Curve Range	[ ]
Lower Limit of Quantification	— ng/mL
Intra-day Precision	[ ]
Inter-day Precision	[ ]
Accuracy	[ ]
Recovery	[ ]
Specificity	No cross reactivity [ ] }
Dilutional Linearity	[ ] <sup>1</sup> [ ] <sup>1</sup>
Stability	[ ] <sup>1</sup> 2-8°C

<sup>a</sup> F0174g assumed - [ ]

<sup>b</sup> F0183g

<sup>c</sup> F0188g

<sup>d</sup> F0317g

<sup>e</sup> F0580g assumed - [ ]

<sup>f</sup> F0375g

<sup>g</sup> F0632g

<sup>h</sup> F0671g

<sup>i</sup> 1419

<sup>j</sup> Calculated %RE (mean/theoretical -1) [ ]

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