

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-839**

**Statistical Review(s)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 21-839

**Drug Name:** Increlex (mecasermin [RDNA origin] injection)  
Recombinant Human Insulin-Like Growth Factor-1 (rhIGF-1)

**Indication(s):** Primary insulin-like growth factor-1 deficiency (IGFD)

**Applicant:** Tercica

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**Review Priority:** Priority (6-month) review

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## 1. EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

The statistical interpretation of the primary endpoint (change in height velocity) and other endpoints was complicated by the uncontrolled, longitudinal nature of the data and the varying lengths of exposure to mecasestermin treatment (range <1 to 11.5 years). Still, it is possible to draw particular statistical conclusions about the effect of mecasestermin on height and other secondary endpoints.

Mecasermin treatment was associated with statistically significant increases in height compared with pre-dose increases in height (Table 1). After one year of mecasestermin treatment, height increased a mean of 5.2 cm/year over the pre-dose growth rate ( $p < .001$ ). Annual height increases were not as dramatic in subsequent years but still significant compared to pre-dose growth rates for patients remaining on treatment ( $p < .001$  through year 6). Results were similar across cohorts defined by the same patients over time (constant sample size across treatment years).

**Table 1. Descriptive statistics for annualized height velocity (cm/yr) observed cases**

	Pre-dose	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
<b>Observed cases</b>									
N	58	58	48	38	23	21	20	16	13
Mean (SD)	2.8 (1.8)	8.0 (2.2)	5.8 (1.5)	5.5 (1.8)	4.7 (1.6)	4.7 (1.6)	4.8 (1.5)	4.6 (1.5)	4.3 (1.1)
Median	2.7	8.3	5.8	5.5	5.0	4.9	4.6	4.1	4.5
Min, Max	0.0, 7.7	1.8, 12.8	1.5, 8.9	2.2, 10.8	2.0, 7.7	2.1, 8.3	2.7, 8.5	2.4, 7.2	2.6, 5.8
Mean (SD) for change from pre-dose	N/A	5.2 (2.6)	2.9 (2.4)	2.3 (2.4)	1.5 (2.2)	1.5 (1.8)	1.5 (1.7)	1.0 (2.1)	0.7 (2.5)
P-value for change from pre-dose	N/A	<0.0001	<0.0001	<0.0001	0.0045	0.0015	0.0009	0.0897	0.3059
95% CI for change from pre-dose	N/A	(4.5, 5.9)	(2.2, 3.6)	(1.6, 3.1)	(0.5, 2.4)	(0.6, 2.3)	(0.7, 2.3)	(-0.2, 2.1)	(-0.8, 2.3)

Results for height velocity SD score, an endpoint that adjusts for changes in height that due to sex and age-related changes in growth, i.e., puberty, were similar to results for height velocity.

Height SD was also significantly increased on mecasestermin compared to the enrollment height SD. Height SD served as another confirmatory endpoint since changes from pre-dose could be assessed based on a single pre-enrollment height measurement without having to rely on pre-dose growth rates which were calculated locally, not at the primary centers. This result allayed concerns about the retrospective nature and quality of the pre-dose growth information and its possible impact on the results for both height velocity and height velocity SD compared to pre-dose rates.

First-year height velocity change from baseline was significantly related to the average dose of mecasestermin. On average, an additional increase of 1 cm/yr of height was achieved for every dose increase of 30  $\mu\text{g}/\text{kg}$ . Greater  $\mu\text{g}/\text{kg}$  doses were given in subsequent years to produce the growth effects seen after in the first year.

(see Section 3.1 – mecaseimerin dose).

Patients enrolled in Study 0671g (n=23) underwent a “stricter protocol” than patients enrolled subsequently. The sponsor claimed that baseline and Year 1, 2 and 3 height velocities were “similar” in the two cohorts (June 20, 2005 submission). The sponsor did not evaluate changes from baseline. This reviewer analyzed first year change from baseline and found a significant difference (p=0.021) for height velocity change from baseline and a statistical trend (p=0.105) for height velocity SD change from baseline (Table below).

**First year height velocity by Study 0671g enrollment (Y/N)**

	Study 0671g (n=23)	Study 1419 only (n=35)	Diff
<u>Mecasermin dose (µg/kg)</u>			
Mean (SD)	89 (24)	111 (20)	-22
Median	91	120	-29
<u>Height velocity (cm/yr)</u>			
Baseline mean (SD)	3.25 (1.97)	2.50 (1.69)	+0.75
Year 1 mean change from baseline (SD)	+4.24 (2.49)	+5.84 (2.54)	-1.61 p=0.021
<u>Height velocity SD</u>			
Baseline mean (SD)	-2.75 (1.73)	-3.64 (1.57)	+0.89
Year 1 mean change from baseline (SD)	+4.36 (3.43)	+5.71 (2.76)	-1.35 p=0.105

## IGF-1

Pharmacokinetic samples of IGF-1 were measured before and/or 2 hours after IGF-1 dosing in 34 patients. Data collection times varied significantly from patient to patient. Samples were collected at roughly 3 to 6 month intervals typically for one to two years beginning 0 to 4½ years after the initiation of treatment (See Figures 2 and 3). Median 2-hour post-dose IGF-1 levels were increased over pre-dose levels (p=.0002 signed rank test). The increase was driven by a cohort of 11 patients whose samples were measured at least 3 years after the start of treatment. IGF-1 levels did not increase in patients treated with mecaseimerin for less than 3 years, a largely different cohort of 15 patients. It is left to clinical to judge whether treatment duration and related confounders such as age and dose explain these results.

## Bone age

Bone age trended towards a significant increase relative to change in chronological age (5.3 yrs vs 4.9 yrs, p=.07) (Table below). The Table also shows bone age results sub-grouped by the median change in age, a rough surrogate for treatment duration. This sub-grouping was suggested by a visual inspection of the data which showed two distinct clusters of patients (see sponsor’s Figure 11.9-1 in this review). Patients below

the median (consisting entirely of ongoing patients new to Study 1419) had a statistically greater change in bone age (2.8 years) compared to the change in chronological age (2.0 years) ( $p=.025$ ). On average, bone age advanced almost a year beyond the increase in chronological age, a 40% increase beyond the change in chronological age. The results for the subgroup were more striking when excluding data from the two patients with negative changes in bone age ( $p=.009$ ) or all four patients with non-positive changes ( $p=.002$ ). Clearly these data require a careful interpretation since cohorts are defined (roughly) by duration of treatment and not by randomized groups.

**Bone age results at last measurement overall and subgrouped by median change in chronological age**

	Bone age (yrs)	Chron age (yrs)
<u>All patients (n=49)</u>		
Mean at baseline <sup>1</sup>	4.26	7.10
Change from baseline <sup>2</sup> (SD)	+5.34 (3.43)	+4.87 (3.37)
Difference (95% CI)	0.47 (-0.04, 0.98)	
	p=.07	
<u>Below the median age change (n=25)</u>		
Mean at baseline	4.09	7.10
Change from baseline (SD)	+2.82 (2.08)	+2.02 (0.79)
Difference (95% CI)	0.80 (0.09, 1.51)	
	p=.025	
<u>Greater than the median age change (n=24)</u>		
Mean at baseline	4.44	7.11
Change from baseline (SD)	+7.97 (2.43)	+7.85 (2.23)
Difference (95% CI)	0.12 (-0.60, 0.85)	
	p=.74	

1 Baseline refers to initial bone age which was evaluated after the start of treatment in a minority of patients.

2 Change calculated as difference between final and initial bone age measurements.

**Antibodies**

Antibodies to IGF-1 treatment were measured in 23 patients. Long term height changes were compared between patients with and without positive antibodies during the first year. Long-term height changes were not different for patients with and without antibodies during the first year. However, the long-term clinical course with respect to height was more variable for patients with positive antibodies during the first year.

## 1.2 Brief Overview of Clinical Studies

Five clinical studies (206s, 375g, 632g, 671g and 1419) were conducted to evaluate the safety and efficacy of Increlex (mecasermin) in children with short stature due to primary insulin-like growth factor-1 deficiency (Primary IGFD). Studies 206s, 375g, 632g and 671g have completed. Study 1419 is ongoing. Data were submitted as of December 31, 2003. The primary efficacy endpoint in all studies was the change from baseline in height velocity. Table 2 lists the studies and major design characteristics.

Some patients were treated across multiple studies, transferring from one protocol to another as a study ended. In particular, all patients in Studies 206s, 375g and 632g later enrolled in Study 671g. All patients except one in Study 671g later enrolled in Study 1419.

**Table 2. Efficacy studies: Major design characteristics**

Trial # Primary centers Dates	# treated/ trt naïve	Daily BID dose of mecasermin	Design Primary endpoint	Duration
0206s UNC 5/91 – 12/95	8 / 8	80 to 120 µg/kg	OL, IS Change in ht velocity	24 months
0375g CHMCC 8/92 – 3/96	8 / 8	80 to 120 µg/kg	R, PC, DB, CO Change in ht velocity	15 months blinded 12 months OL
0632g CHMCC 7/94 – 2/96	6 / 5 <sup>1</sup>	60 µg/kg	OL Change in ht velocity	12 months
0671g UNC, CHMCC 11/95 – 6/98	23 / 2 <sup>2</sup>	80 to 120 µg/kg	OL Change in ht velocity	24 months
0930s (1419) UNC, CHMCC 5/98 - present	71 / 41 <sup>3</sup>	60 to 120 µg/kg	OL, IS Change in ht velocity	Long-term (ongoing)

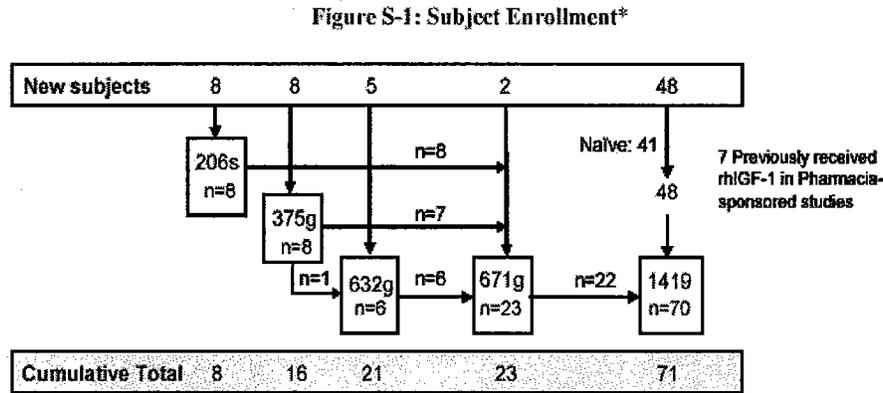
R = randomized, PC = placebo-controlled, DB = double-blind, CO = crossover, OL = open label, IS = investigator-sponsored, UNC = University of North Carolina at Chapel Hill, CHMCC = Children's Hospital Medical Center Cincinnati

<sup>1</sup> Includes 1 patient from study 375g

<sup>2</sup> Includes 21 patients from studies 375g, 206s and 632g

<sup>3</sup> Includes 22 patients from study 671g. Enrollment as of December 31, 2003.

Sponsor's Figure S-1 is a schematic of patient enrollment across studies.



Major highlights of the studies are:

- 206s was an investigator-sponsored open-label study of mecaseimerin in 8 patients.
- 375g was a randomized, placebo-controlled, double-blind, crossover study in 8 patients. Four patients completed both mecaseimerin and placebo treatment periods.
- 632g was an open-label study in 6 patients (5 naïve patients and one patient from Study 375g) designed in response to a request by FDA to evaluate a lower dose (60 µg/kg) of mecaseimerin.
- 671g was an open-label, multi-center trial of mecaseimerin in 23 patients. Twenty-one (21) patients were rolled over from prior studies and two patients were naïve. Patients had completed 2 years of treatment when the study was terminated due to the closure of the mecaseimerin diabetes program at Genentech.
- 1419 is an ongoing investigator-sponsored, open-label trial. Patients treated with mecaseimerin in previous Genentech-sponsored growth studies and patients naïve to mecaseimerin were enrolled in Study 1419 after the termination of Study 671g.

The 23 patients enrolled through Study 671g used “a more stringent protocol” than patients who were enrolled subsequently (20 June 2005 secure e-mail submission submitted to eCTD on June 29, 2005). Naive patients enrolled in Study 1419 after 1998 were dose titrated and followed-up by local endocrinologists so labs and special study procedures were not available.

Total mecaseimerin exposure across the five studies was 71 patients. Median exposure was 3 years (range <1 to 11.5 yrs). Sixty-one (61) patients completed at least 1 year of treatment. Fifty-eight (58) patients had a pre-treatment height velocity. The Table below shows the number of patients with height data at pre-treatment and after the indicated number of years on treatment.

Years	1	2	3	4	5	6	7	≥8
# patients <sup>1</sup>	58	48	38	23	21	20	16	13

<sup>1</sup> On treatment with pre-treatment and annual height velocity data

### 1.3 Statistical Issues and Findings

Patients were enrolled in multiple studies and received some continuity of treatment across studies through annual visits at the two primary enrolling centers, UNC (Dr. Underwood) and CHMCC (Dr. Chernausek). Following the sponsor’s approach, it seemed reasonable to analyze patients as though they were enrolled in a single study. Individual study results were analyzed as appropriate. For example, the crossover study 375g was the only study with a control group. It was analyzed separately in addition to being combined with the other studies. Also, on occasion this reviewer presented data separately by primary enrolling center (UNC or CHMCC) when appropriate. The sponsors did not present data separately by center.

The statistical analysis and interpretation of the results was complicated by the uncontrolled, longitudinal nature of the data and the varying lengths of exposure to mecaseimerin treatment. Analyses of within-patient changes for height velocity and other continuous variables were performed whenever possible. Many of the analyses involved the one-year time point since dropouts could potentially bias the analysis of data involving longer exposures. Other time points were analyzed as appropriate.

The analysis of the IGF-1 pharmacokinetic data was particularly complicated, specifically by the irregular nature of the sampling process (Figures 2 and 3). Patients had multiple IGF-1 values measured at varying intervals. The timing of the first PK measurement was variable relative to the start of mecaseimerin treatment, e.g., some patients had IGF-1 levels only during the first 3 years of treatment whereas other patients had their first measurement after 3 and 4 years. The sponsor analyzed pre-and post dose levels separately, pooling data across patients and time points ignoring both the paired and repeated measures aspects of the data. This reviewer’s analysis of the data focused on the within patient IGF-1 differences (post-dose minus pre-dose).

Multiple differences within a patient were averaged to a single value for each patient to maintain the patient as the unit of analysis.

This reviewer corrected several other presentations by the sponsor based on either different data (hypoglycemia) or incorrect analyses (GFR).

## 2. INTRODUCTION

### 2.1 Overview

Mecasermin is intended for use as replacement therapy in the long-term treatment of growth failure in children with primary IGF-1 deficiency (Primary IGFD). IGF-1 is needed in normal levels to stimulate appropriate bone, cartilage and organ growth. Growth hormone (GH) can be used to stimulate IGF-1 production in most children. In children with Primary IGFD, GH cannot be used to raise levels of IGF-1 since there is an insensitivity to the effects of GH rather than a deficiency of GH.

The primary inclusion criteria for the 5 studies were:

- Height SD score < -2
- Evidence that short stature would not be effectively treated by GH
  - GH sufficiency or
  - Non-responsiveness to GH treatment or
  - GH deletion together with antibodies to GH
- Pre-dose SD score < -2 for patients with GH sufficiency

Mecasermin has a relatively short estimated half-life of 5.8 hours (n=3).

The Medical Division (HFD-510) granted priority review status based on an unmet medical need.

### 2.2 Data Sources

Datasets and Final reports for the integrated data used by this reviewer are located at the following links.

<\\Cdsub1\evsprod\n021839\0000\m5\53-clin-stud-rep\537-crf-ip\integrated-analysis-datasets>

<\\Cdsub1\evsprod\n021839\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\primary-igf-deficiency>

The sponsor submitted e-mail responses to clinical and statistical questions on June 20, 2005.

### 3. STATISTICAL EVALUATION

#### Baseline and Demographic variables

The sponsor's Table 11.1-2 below shows baseline and demographic characteristics for numeric variables for patients with at least one year of treatment (n=61). The mean age was 6.7 years. The mean height SD score at baseline was -6.7 indicating extreme short stature. The average height was just under 3 feet.

**Sponsor's Table 11.1-2. Demographics and Baseline Characteristics for numeric variables (patients with  $\geq$  One Year of Treatment n=61)**

	N	Mean	SD	Min	Max
Age (years)	61	6.7	3.8	1.7	15.2
Height (cm)	61	84.5	15.3	61.3	133.1
Height SD Score	61	-6.7	1.8	-12.1	-2.8
Pre-Treatment Height Velocity (cm/yr)	58	2.8	1.8	0.0	7.7
Pre-Treatment Height Velocity SD Score	58	-3.3	1.7	-6.6	0.9
Baseline IGF-1 (ng/mL)	56	21.6	20.6	0.2	82.1
Baseline IGF-1 SD Score	56	-4.3	1.6	-9.5	-0.7
Weight (kg)	59	12.5	6.0	5.8	35.0
BMI (kg/m <sup>2</sup> )	59	16.5	2.5	12.8	24.6
BMI SD Score	57	-0.2	1.2	-3.1	2.2
Bone Age (years)	57	4.2	2.8	0.3	12.3
Maximum IGF-1 Concentration from IGF-1 Gen Test (ng/mL)	36	21.9	24.8	0.5	115.0
Maximum IGF-1 SD Score from IGF-1 Gen Test	36	-4.5	1.9	-8.9	-0.5
Maximum Growth Hormone Concentration (ng/mL)	55	55.7	46.2	0.5	209.0

Appendix 1 shows the continuous baseline and demographic data by primary center. Baseline IGF-1 mean values (raw and SD) values were statistically higher at CHMCC than at UNC. BMI z-scores were statistically lower at CHMCC. The distributions for all other variables were comparable at the two centers.

Table 3 shows demographic data for categorical variables for all randomized patients (n=71). Patients were mostly male (61%) and Caucasian (82%). Fifty-six (56) of 61 patients with first-year data were reported or imputed to be pre-pubertal at entry. Patients were enrolled from 21 countries.

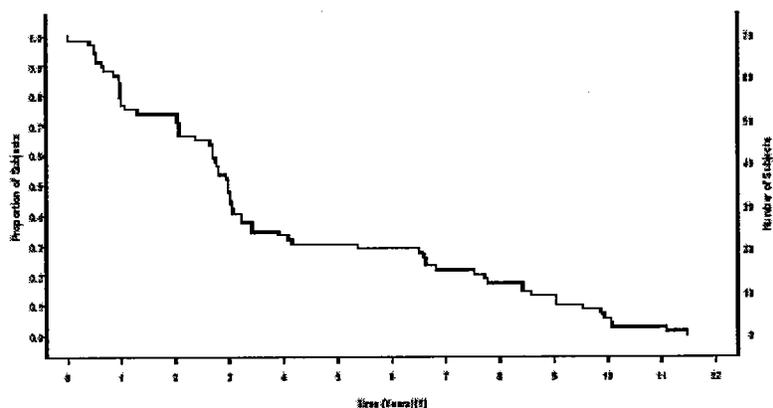
**Table 3. Demographics and Baseline Characteristics for categorical variables (all randomized patients n=71)**

Variable	UNC N=58	CHMCC N=13	Total N=71
<u>Sex</u>			
Male	34 (59%)	9 (69%)	43 (61%)
Female	24 (41%)	4 (31%)	28 (39%)
<u>Race</u>			
Caucasian	50 (86%)	8 (62%)	58 (82%)
African American	1 (2%)	2 (15%)	3 (4%)
Asian	3 (5%)	0	3 (4%)
Hispanic	3 (5%)	3 (23%)	6 (9%)
Pakistani	1 (2%)	0	1 (1%)
<u>Disease type</u>			
Laron type	51 (88%)	10 (77%)	61 (86%)
Gene deletion type	5 (9%)	3 (23%)	8 (11%)
Isolated generalized GH deficiency	1 (2%)	0	1 (1%)
GH antibodies	1 (2%)	0	1 (1%)
<u>Baseline Tanner</u>			
Stage 1	48 (83%)	13 (100%)	61 (86%)
Stage 2	1 (2%)	0	1 (1%)
Missing	9 (15%)	0	9 (13%)
<u>Country</u>			
Saudi Arabia	16 (28%)	0	16 (23%)
US	8 (14%)	4 (31%)	12 (17%)
Italy	8 (14%)	2 (15%)	10 (14%)
Argentina	6 (10%)	1 (8%)	7 (10%)
Other (17 countries)	20 (34%)	6 (46%)	26 (36%)
<u>Previous mecaseerin therapy</u>			
No	51 (88%)	13 (100%)	64 (90%)
Yes	7 (12%)	0	7 (10%)

## Disposition

Sponsor's Figure 13.1-1 shows a Kaplan-Meier plot of treatment duration. The median treatment duration was 3.0 years. Durations were shorter at UNC (2.7 yrs) than CHMCC (9.0 yrs).

**Figure 13.1-4: Kaplan-Meier Plot of Mecasermin Treatment Duration- All Subjects (n=71)**



Source: Appendix 16.2.11.2

[1] Number of years from time of first dose of mecasermin therapy to time of last height measurement

Fifty-three (53) of the 71 enrolled patients were ongoing as of the data cutoff date for the submission (December 31, 2003). Reasons for discontinuation (including study completion) for the remaining 18 patients are shown in Table 4.

**Table 4. Reasons for discontinuation**

Reason for discontinuation	N (%)
Lost to F/U	5 (28%)
Non-compliance	5 (28%)
"Patient completed"	5 (28%)
"Completion"	1 (5%)
Parent/ patient decision	1 (5%)
Other	1 (5%)
Total discontinuations	18 (100%)

### 3.1 Evaluation of Efficacy

#### Methods

##### Height

Height measurements for the first cohort of patients (n=23) were performed at the 2 primary centers, UNC and CHMCC. Wall-mounted stadiometers were used to measure height. Measurements were performed every 6 months through the completion of Study 671g and annually after these subjects were enrolled in Study 1419. Interval height measurements for these patients were also performed by the local referring pediatric

endocrinologists and were used as “supporting information” but were not used in the efficacy analysis. Since 1998 height measurements performed for subjects not seen at UNC or CHMCC were performed by the local referring pediatric endocrinologist and were also used in the analysis of efficacy.

The sponsor did not have access to the actual pre-treatment height measurement data, only the treatment height velocity as calculated by the local referring endocrinologist (June 20, 2005, submission). Because the pre-treatment growth velocity data were potentially of different quality compared to prospective data collected on treatment, height SD scores, which didn't rely on retrospective data calculations, served as a check on the results on growth velocity changes from baseline.

For the 4 patients in the crossover Study 375g randomized to the placebo/ mecasermin treatment sequence, baseline height velocity was calculated based on height measurements during the placebo period.

#### Height interpolation

Heights were not always measured at exact one-year intervals. The sponsor calculated annual heights by interpolating between the closest date before the annual date and the closest date after the annual date. These interpolated heights were used in computing annual height velocities, height velocity SD scores and height SD scores. If height was not measured after a given annual date, the height from the closest date prior to the date was used in computing the annualized height velocity, height velocity SD score, and height SD score provided the date was within 90 days of the annual date.

Patients without a baseline height used the first post-baseline height when computing the first year annualized height velocity.

#### Data analysis

The sponsor performed statistical comparisons using paired t tests for changes from baseline or 2-sample t tests when comparing the results in subgroups. The sponsor did not present any data separately by center.

As mentioned in Section 1.3 (Statistical Issues and Findings), the sponsor analyzed pre- and post dose IGF-1 levels separately, pooling data across patients and time points and ignoring both the paired and repeated measures aspects of the data. Based on conversations with the FDA Medical Officer, this reviewer's analysis of the data focused on the within patient IGF-1 differences (post-dose minus pre-dose). Multiple differences within a patient were averaged to a single value for each patient to maintain the patient as the unit of analysis. These data were analyzed by the signed rank test.

## Results

### Mecasermin dose

Table 5 shows summary data for mecaseerin dose overall and by primary center. Sample sizes are shown at each time point through Year 8. Sample sizes were not constant over time since patient exposure varied. CHMCC patients were initially dosed lower than UNC patients primarily due to the dosing regimen in CHMCC Study 632g (n=6) which used a low starting dose of 60 µg/kg. Dosing at the 2 centers was similar by Year 3. The median dose for all patients was at or near 120 µg/kg at all time points.

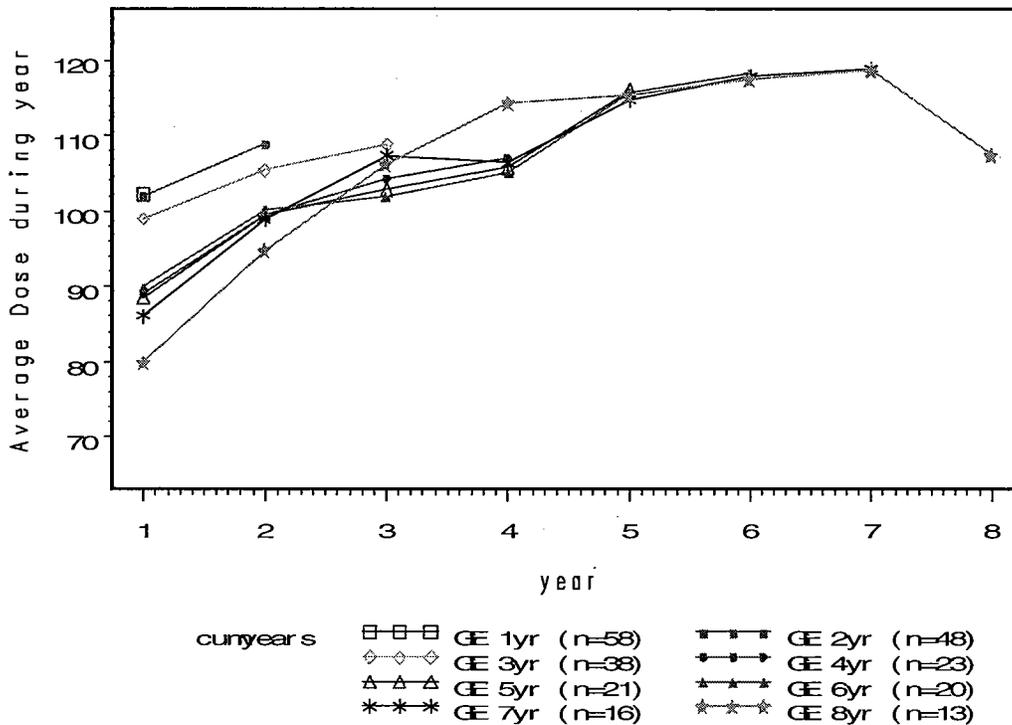
**Table 5. Summary data for Mecasermin dosing (µg/kg)**

	UNC			CHMCC			Total		
	n	Mean	Median	N	Mean	median	n	Mean	median
Year 1	45	111	120	13	73	62	58	102	119
Year 2	35	117	120	13	88	81	48	109	120
Year 3	25	107	120	13	111	119	38	109	120
Year 4	10	92	98	13	119	120	23	107	120
Year 5	9	117	120	12	115	120	21	116	120
Year 6	9	120	120	11	117	120	20	118	120
Year 7	6	119	120	10	119	120	16	119	120
Year 8	3	98	120	10	110	120	13	107	120

Average and median doses were relatively stable over time although doses were generally increased over time for individual patients. This seemingly contradictory finding is due to the fact that time on study correlated with starting dose, i.e., patients who remained on treatment the longest generally started at lower doses. This is not easily discernable from Table 5 but is illustrated in Figure 1. Each curve shows the mean dose over time for the same cohort of patients. The length of a curve corresponds to a given minimum number of years on study (at least 1 year, 2 years, 3 years, etc.). The curves represent overlapping cohorts of patients; each curve (except the shortest one) represents a subset of patients from the next longer curve. The mean doses in Table 5 correspond to the terminal points of the eight curves.

Figure 1 parallels the presentation of height velocity in Table 6 (later in the review) in that the data are presented by overlapping cohorts defined by minimum treatment duration. Figure 1 and Table 6 together show that greater doses on a µg/kg basis were given over time to sustain the observed linear growth effects.

Figure 1  
Average dose (mcg/kg)  
By minimum total years of treatment



## Height velocity

Table 6 shows data on the primary endpoint, height velocity. Data are presented by overlapping cohorts defined by minimum treatment duration. Fifty-six (56) of the 61 (92%) patients with first-year data were reported or imputed as pre-pubertal at baseline. Therefore, height velocity over time are confounded with growth changes occurring at puberty.

First-year height increased a mean of 5.2 cm/year over the pre-dose growth rate ( $p < .001$ ). Results were similar across cohorts defined by the same patients over time (constant sample size across treatment years).

First-year height velocity was negatively correlated with baseline height velocity ( $r = -.55$ ,  $p < .001$ ). Patients with large baseline changes in height velocity had smaller benefits from treatment than patients with smaller changes in height velocity prior to treatment. Seven patients had previous treatment with IGF-1. None of these patients had on-treatment height velocity data at one year.

**Table 6. Annualized height velocity by number of years treated**

	Pre-dose	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
<b>Subjects Completing 1 Year</b>									
N	58	58							
<b>Mean (SD)</b>	<b>2.8 (1.8)</b>	<b>8.0 (2.2)</b>							
Median	2.7	8.3							
Min, Max	0.0, 7.7	1.8, 12.8							
Mean (SD) for change from pre-dose	N/A	5.2 (2.6)							
P-value for change from pre-dose [1]	N/A	<0.0001							
95% CI for change from pre-dose	N/A	(4.5, 5.9)							
<b>Subjects Completing 2 Years</b>									
N	48	48	48						
<b>Mean (SD)</b>	<b>2.9 (1.9)</b>	<b>8.2 (2.2)</b>	<b>5.8 (1.5)</b>						
Median	2.7	8.7	5.8						
Min, Max	0.0, 7.7	2.4, 12.8	1.5, 8.9						
Mean (SD) for change from pre-dose	N/A	5.3 (2.5)	2.9 (2.4)						
P-value for change from pre-dose [1]	N/A	<0.0001	<0.0001						
95% CI for change from pre-dose	N/A	(4.5, 6.0)	(2.2, 3.6)						
<b>Subjects Completing 3 Years</b>									
N	38	38	38	38					
<b>Mean (SD)</b>	<b>3.1 (1.9)</b>	<b>8.0 (2.4)</b>	<b>5.8 (1.3)</b>	<b>5.5 (1.8)</b>					
Median	3.0	8.3	5.9	5.5					
Min, Max	0.0, 7.7	2.4, 12.8	2.7, 8.4	2.2, 10.8					
Mean (SD) for change from pre-dose	N/A	4.9 (2.5)	2.7 (2.3)	2.3 (2.4)					
P-value for change from pre-dose [1]	N/A	<0.0001	<0.0001	<0.0001					
95% CI for change from pre-dose	N/A	(4.1, 5.7)	(2.0, 3.4)	(1.6, 3.1)					
<b>Subjects Completing 4 Years</b>									
N	23	23	23	23	23				
<b>Mean (SD)</b>	<b>3.2 (2.0)</b>	<b>7.5 (2.6)</b>	<b>5.8 (1.3)</b>	<b>5.0 (1.4)</b>	<b>4.7 (1.6)</b>				
Median	2.7	7.9	5.8	5.2	5.0				
Min, Max	0.2, 7.7	2.4, 12.8	3.6, 8.2	2.2, 7.6	2.0, 7.7				
Mean (SD) for change from pre-dose	N/A	4.2 (2.5)	2.6 (2.5)	1.7 (2.2)	1.5 (2.2)				
P-value for change from pre-dose [1]	N/A	<0.0001	<0.0001	0.0008	0.0045				
95% CI for change from pre-dose	N/A	(3.2, 5.3)	(1.5, 3.7)	(0.8, 2.7)	(0.5, 2.4)				
<b>Subjects Completing 5 Years</b>									
N	21	21	21	21	21	21			
<b>Mean (SD)</b>	<b>3.2 (2.0)</b>	<b>7.6 (2.6)</b>	<b>5.8 (1.3)</b>	<b>5.0 (1.5)</b>	<b>4.7 (1.5)</b>	<b>4.7 (1.6)</b>			
Median	2.7	7.9	5.8	5.2	5.0	4.9			
Min, Max	0.2, 7.7	2.4, 12.8	3.6, 8.2	2.2, 7.6	2.0, 7.7	2.1, 8.3			
Mean (SD) for change from pre-dose	N/A	4.3 (2.6)	2.6 (2.5)	1.7 (2.1)	1.5 (2.3)	1.5 (1.8)			
P-value for change from pre-dose [1]	N/A	<0.0001	0.0001	0.0014	0.0089	0.0015			
95% CI for change from pre-dose	N/A	(3.1, 5.5)	(1.4, 3.7)	(0.7, 2.7)	(0.4, 2.5)	(0.6, 2.3)			
<b>Subjects Completing 6 Years</b>									
N	20	20	20	20	20	20	20		
<b>Mean (SD)</b>	<b>3.3 (2.0)</b>	<b>7.5 (2.7)</b>	<b>5.7 (1.3)</b>	<b>5.0 (1.5)</b>	<b>4.8 (1.5)</b>	<b>4.8 (1.5)</b>	<b>4.8 (1.5)</b>		
Median	3.2	7.9	5.7	5.2	5.0	4.9	4.6		
Min, Max	0.2, 7.7	2.4, 12.8	3.6, 8.2	2.2, 7.6	2.0, 7.7	2.1, 8.3	2.7, 8.5		
Mean (SD) for change from pre-dose	N/A	4.2 (2.6)	2.4 (2.5)	1.7 (2.2)	1.5 (2.4)	1.5 (1.9)	1.5 (1.7)		
P-value for change from pre-dose [1]	N/A	<0.0001	0.0003	0.0024	0.0118	0.0016	0.0009		
95% CI for change from pre-dose	N/A	(3.0, 5.5)	(1.3, 3.6)	(0.7, 2.7)	(0.4, 2.6)	(0.7, 2.4)	(0.7, 2.3)		
<b>Subjects Completing 7 Years</b>									
N	16	16	16	16	16	16	16	16	
<b>Mean (SD)</b>	<b>3.6 (2.1)</b>	<b>7.5 (2.8)</b>	<b>5.6 (1.2)</b>	<b>4.9 (1.5)</b>	<b>4.4 (1.4)</b>	<b>4.7 (1.7)</b>	<b>4.9 (1.6)</b>	<b>4.6 (1.5)</b>	
Median	3.8	7.9	5.5	5.1	4.3	4.7	4.8	4.1	
Min, Max	0.5, 7.7	2.4, 12.8	3.8, 7.9	2.2, 7.6	2.0, 7.2	2.1, 8.3	2.7, 8.5	2.4, 7.2	
Mean (SD) for change from pre-dose	N/A	3.8 (2.6)	2.0 (2.6)	1.3 (2.2)	0.8 (2.1)	1.1 (1.7)	1.3 (1.6)	1.0 (2.1)	
P-value for change from pre-dose [1]	N/A	<0.0001	0.0063	0.0325	0.1428	0.0184	0.0047	0.0897	
95% CI for change from pre-dose	N/A	(2.5, 5.2)	(0.7, 3.4)	(0.1, 2.4)	(-0.3, 1.9)	(0.2, 2.0)	(0.5, 2.2)	(-0.2, 2.1)	
<b>Subjects Completing 8 Years</b>									
N	13	13	13	13	13	13	13	13	13
<b>Mean (SD)</b>	<b>3.6 (2.3)</b>	<b>7.0 (2.9)</b>	<b>5.3 (1.0)</b>	<b>5.0 (1.4)</b>	<b>4.5 (1.5)</b>	<b>4.7 (1.8)</b>	<b>4.9 (1.7)</b>	<b>4.3 (1.3)</b>	<b>4.3 (1.1)</b>
Median	3.6	6.4	5.3	5.2	4.4	4.9	4.8	3.7	4.5
Min, Max	0.5, 7.7	2.4, 12.8	3.8, 7.2	2.8, 7.6	2.0, 7.2	2.1, 8.3	2.7, 8.5	2.4, 6.4	2.6, 5.8
Mean (SD) for change from pre-dose	N/A	3.4 (2.7)	1.8 (2.8)	1.4 (2.2)	0.9 (2.2)	1.2 (1.8)	1.3 (1.8)	0.7 (2.3)	0.7 (2.5)
P-value for change from pre-dose [1]	N/A	0.0006	0.0400	0.0425	0.1562	0.0387	0.0206	0.2624	0.3059
95% CI for change from pre-dose	N/A	(1.8, 5.0)	(0.1, 3.4)	(0.1, 2.7)	(-0.4, 2.3)	(0.1, 2.3)	(0.2, 2.4)	(-0.6, 2.1)	(-0.8, 2.3)

[1] p-values computed using paired-t test

Table 7 shows first-year height velocity by country (US, Saudi Arabia, Argentina, Italy, other). OTHER included all countries with 3 or fewer patients. Saudi Arabia had the greatest mean change from baseline (+6.0 cm/year). US and Argentine patients had the least favorable changes, +4.2 and +3.8 cm/year, respectively. Changes were significant within each country ( $p < .01$ ).

**Table 7. First year height velocity and SD scores by country**

	Saudi Arabia (n=14)	US (n=12)	Italy (n=5)	Argen Tina (n=6)	Other (n=21)
<b>Height velocity</b>					
Pre-dose mean (SD)	2.8 (1.8)	3.2 (1.5)	1.9 (0.8)	2.9 (2.0)	2.8 (2.2)
median	2.7	3.5	2.0	3.0	2.3
Mean change from pre-dose (SD)	6.0 (1.9)	4.2 (3.1)	5.9 (2.7)	3.9 (2.4)	5.5 (2.7)
Median	5.8	4.2	5.0	4.4	5.1
<b>Height velocity SD score</b>					
Pre-dose mean (SD)	2.8 (1.8)	3.2 (1.5)	1.9 (0.8)	2.9 (2.0)	2.8 (2.2)
median	2.7	3.5	2.0	3.0	2.3
mean change from pre-dose (SD)	6.0 (1.9)	4.2 (3.1)	5.9 (2.7)	3.9 (2.4)	5.5 (2.7)
median	5.8	4.2	5.0	4.4	5.1

First year height velocity change from baseline was not related to the baseline height SD score ( $p = .69$  regressing change on baseline height SD). This result indicates the magnitude of the treatment effect was not related to the severity of disease at baseline assuming height SD is a proxy for severity of disease.

Nine patients were identified by the FDA Medical Officer as having the wrong entry criteria for the study. This reviewer re-analyzed the height velocity data after removing the nine patients from the analysis. The point estimates in Table 6 for mean annualized growth velocity typically changed by no more than 0.1 cm/year and never by more than 0.2 cm/year.

Table 8 shows first year height velocity and SD scores by center. Results were statistically different between centers on height velocity ( $p = .002$ ) and SD score (nonparametric  $p = .002$ ). The statistical difference was most likely a consequence of under-dosing at CHMCC during the first 2 years. Growth rates were not statistically different between the centers beginning in Year 2.

**Table 8. First year height velocity and SD scores by center**

	UNC (n=45)	CHMCC (n=13)	Mean difference (95% CI)
<b>IGF-1 dose (<math>\mu\text{g}/\text{kg}/\text{day}</math>)</b>			
Mean (SD)	111 (18)	73 (17)	37 (26, 49)
<b>Height velocity</b>			
Pre-dose mean (SD)	2.7 (1.7)	3.2 (2.1)	

median	2.6	2.7	
Mean change from pre-dose (SD)	+5.8 (2.4)	+3.3 (2.6)	2.5 (0.9, 3.9)
Median change	+5.6	+2.8	2.8
<u>Height velocity SD score</u>			
Pre-dose mean (SD)	-3.5 (1.6)	-2.7 (2.0)	
median	-3.4	-2.9	
mean change from pre-dose (SD)	+5.7 (2.7)	+3.4 (3.9)	2.2 (0.4, 4.1)
median change	+6.0	+2.5	3.4

### Study 375g

Study 375g provided placebo-controlled data on mecasermin although in just 4 patients who completed both treatment periods of the crossover design. Table 9 shows height velocity for the 4 patients who completed both treatment periods. Mecasermin was clearly superior to placebo in increasing height velocity except in Patient 18004 who experienced similar increases in height on drug and placebo. Overall, these data are extremely limited and do not contradict the height velocity results for the rest of the patient population based on changes from baseline.

**Table 9. Height velocity in placebo-controlled Study 375g (completers)**

Patient	Baseline Age (yrs)	Treatment sequence	Base Ht SD <sup>2</sup>	Mecasermin		Placebo	
				HV <sup>1</sup>	Ht SD <sup>2</sup>	HV <sup>1</sup>	Ht SD <sup>2</sup>
18001	3.0	P/M	-6.1	7.2	-6.3	0.8	-6.6
18002	13.5	M/P	-7.3	9.8	-7.1	2.2	-7.7
18003	1.7	M/P	NA	7.7	-5.6	2.9	-6.2
18004	4.2	P/M	-4.1	7.7	-3.3	7.6	-3.8

<sup>1</sup> Height velocity (cm/year)

<sup>2</sup> Height standard deviation score

### Relationship between dose and first year height velocity

First year height velocity change from baseline was significantly related to the average dose of mecasermin (p=.015) The fitted linear regression equation was:

$$\text{HV change from baseline (cm/yr)} = 1.638 + 0.035 \cdot \text{dose } (\mu\text{g/kg})$$

From the regression equation, an additional mean increase in height of 1 cm/yr occurred for each dose increase of 30  $\mu\text{g/kg}$ . Females had a greater numerical dose-response than males but the differences did not appear to be meaningful. Females received slightly larger average doses than males (see Section 4.1).

## Height velocity SD scores

Appendix 2 shows height velocity SD presented in a format similar to the layout in Table 6. These data are age and sex-adjusted and therefore largely remove the confounding effects of puberty on growth. According to the sponsor, height velocity was adjusted using data from Tables VIIA (boys) and VIIB (girls) in Tanner, Whitehouse, and Takaishi, "Standards from Birth to Maturity for Height, Weight, Height Velocity, and Weight Velocity: British Children", 1965. *II Arch. Dis. Childhood.*, 1966, 41, 613.

Height velocity SD changes from pre-dose were statistically significant for all cohorts at all interim time points.

## Height SD scores

The Table below shows observed height SD scores over time. Height SD changes from pre-dose were significant at all time points. Results were similar for cohorts defined by treatment duration on study at all interim time points.

	Pre-dose	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
Observed cases									
N	61	61	51	40	24	21	20	16	13
Mean (SD)	-6.7 (1.8)	-5.9 (1.8)	-5.6 (1.8)	-5.4 (1.8)	-5.5 (1.9)	-5.6 (1.8)	-5.4 (1.8)	-5.2 (2.0)	-5.2 (2.0)
Median	-6.5	-5.8	-5.6	-5.5	-5.6	-6.0	-6.2	-5.6	-5.2
Min, Max	-12.1, -2.8	-10.7, -2.2	-9.5, -2.0	-8.8, -2.0	-8.7, -1.7	-8.4, -1.5	-8.2, -1.0	-8.3, -1.1	-8.7, -1.5
Mean (SD) for change from pre-dose	N/A	0.8 (0.5)	1.2 (0.8)	1.4 (1.1)	1.3 (1.2)	1.4 (1.3)	1.4 (1.2)	1.4 (1.1)	1.5 (1.1)
P-value for change from pre-dose	N/A	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001	0.0001	0.0003
95% CI for change from pre-dose	N/A	(0.7, 0.9)	(0.9, 1.4)	(1.1, 1.7)	(0.8, 1.9)	(0.8, 2.0)	(0.8, 1.9)	(0.8, 1.9)	(0.9, 2.2)

## IGF-1 pharmacokinetic data

Trough and 2-hour post-dose PK samples for serum or plasma IGF-1 were collected during the initial in-hospital dose titration and at roughly 3 to 6-month intervals thereafter in Studies 375g, 632g and 671g. Some samples were also collected in patients new to Study 1419. IGF-1 samples in Studies 375g, 632g, and 671g were measured using Genentech's in-house IGF-1 radioimmunoassay.

The baseline (pre-treatment, not PK samples) serum IGF-1 concentration for the purpose of assessing study inclusion was the IGF-1 concentration prior to the first dose of growth hormone in the IGF-1 generation test. If no such concentration was available, the IGF-1 concentration from the pre-IGF-1 (trough) dose from the first PK was used to assess eligibility.

IGF-1 measurements (pre-dose or 2-hours post-dose or both) were collected from 23 patients in Study 671g and 11 patients new to Study 1419. Figures 2 and 3 show pre-dose and 2-hour post-dose sampling times, respectively, relative to the start of IGF-1 treatment. Each line represents one patient; a dot represents the time of PK

evaluation. The number and timing of measurements varied considerably from patient to patient.

Figure 2  
Timing of IGF1 PK pre-dose measurements  
as measured by yrs on treatment  
Lines connect data for same patient

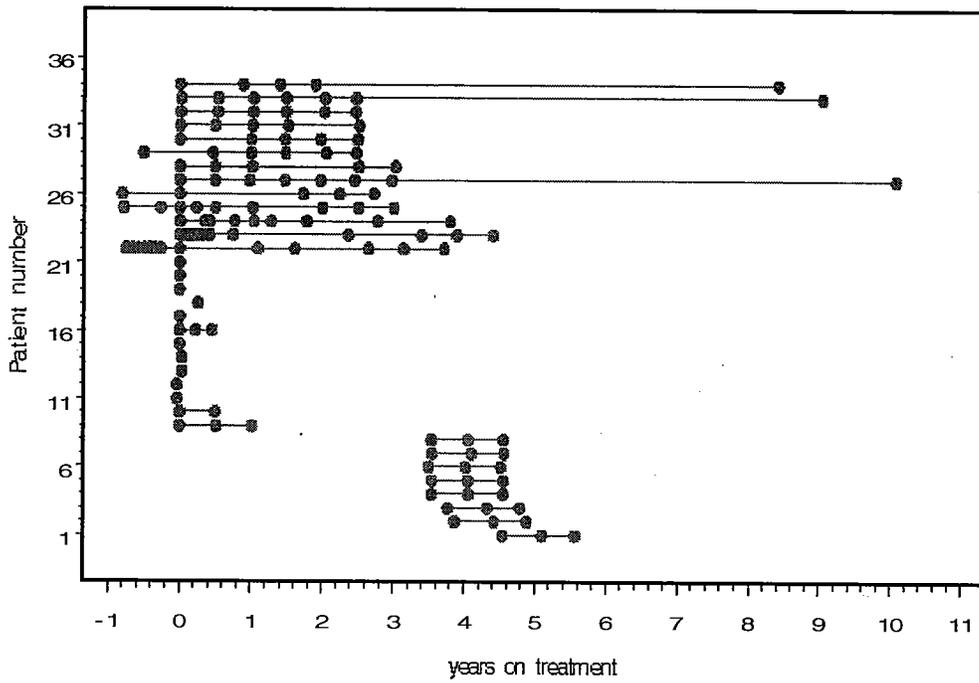


Figure 3  
 Timing of IGF1 PK 2hr post-dose measurements  
 as measured by yrs on treatment  
 Lines connect data for same patient

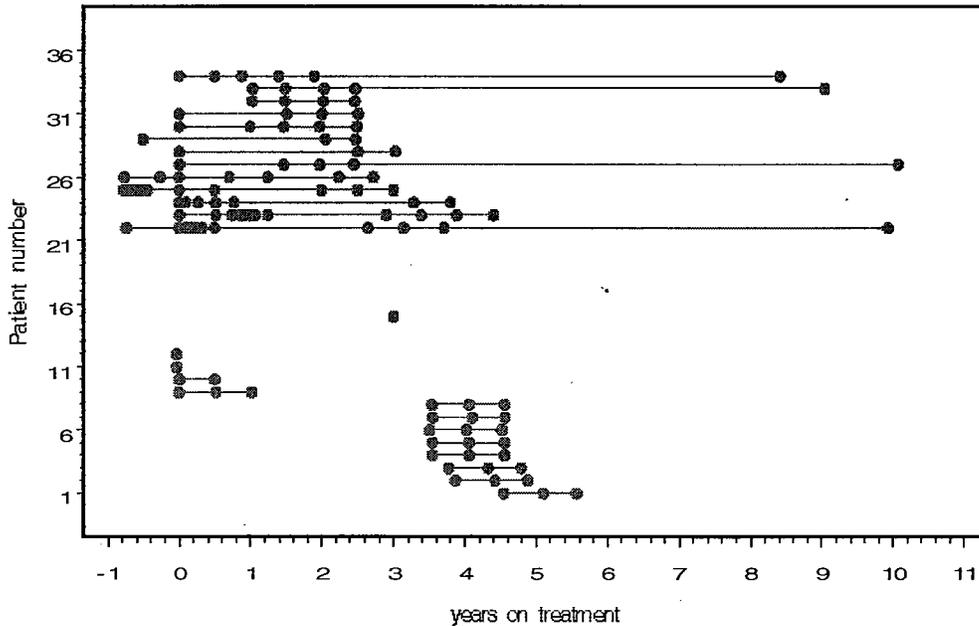


Table 10 shows the sponsor's PK results. Descriptive statistics for pre- and post-dose IGF-1 levels were computed separately, ignoring the natural pairing of these data. Means and standard deviations were calculated by treating each value as an independent observation without accounting for the fact that most patients had multiple pre- and post-dose measurements.

The mean pre-dose IGF-1 level was 52 ng/mL, "abnormally low" according to the sponsor. Post-dose levels were approximately double although SD scores were still in the low range.

**Table 10. Sponsor's PK results for IGF-1 (ng/mL)**

	Pre-dose	Pre-dose SD score	2-hr post-dose		Post-dose SD score	
			80µg/kg	120µg/kg	80µg/kg	120µg/kg
# subjects	34	34	NA <sup>1</sup>	NA	NA	NA
# measurements	164	164	28	81	28	81
Mean	52	-3.6	100	-2.1	128	-1.7
SD	58	3.0	106	2.6	112	2.0

<sup>1</sup> 26 patients had one or more 2-hour post-dose measurements irrespective of dose. The total number of 2-hour post-dose measurements for the 26 patients was n=122.

This reviewer conducted a separate analysis of IGF-1 levels. In consultation with the Medical Officer, Dr. Roman, this reviewer focused on the analysis of the change in each patient from pre- to 2-hour post-dose IGF-1 levels as the most appropriate endpoint in the analysis. Some patients had pre- or post-dose levels but not both. In these cases, a change score was not calculated and was recorded as missing.

Table 11 shows descriptive statistics for change in IGF-1 level (2-hr post-dose minus pre-dose level) by years of treatment rounded to the nearest whole year. Figure 4 shows median IGF-1 changes over time. The patients contributing to the graph at each time point could be quite different. This is an unavoidable aspect of the data due to the irregular nature of the sampling process illustrated in Figures 2 and 3. For example, the group of patients with IGF-1 levels measured during the first 2 years of treatment overlaps only slightly with the group of patients with IGF-1 levels at treatment years 3 and 4.

**Table 11. Descriptive statistics for change in IGF-1 change (post-dose minus pre-dose) by years of treatment**

Years	# pts	Dose (µg/kg)				IGF-1 (ng/mL)			
		Mean	Med	Min	Max	Mean	Med	Min	Max
-1 <sup>2</sup>	3	93	100	80	100	22	21	1	43
0	14	87	90	60	120	66	17	-27	399
1	9	96	100	60	120	28	-2	-41	299
2	9	119	120	120	120	-8	-23	-55	140
3	6	120				95	119	-25	166
4	10					71	85	-28	137
5	8					90	91	8	143
6	1					110			
7	0								
8	1	120				322			
9	1					369			
10	1					417			

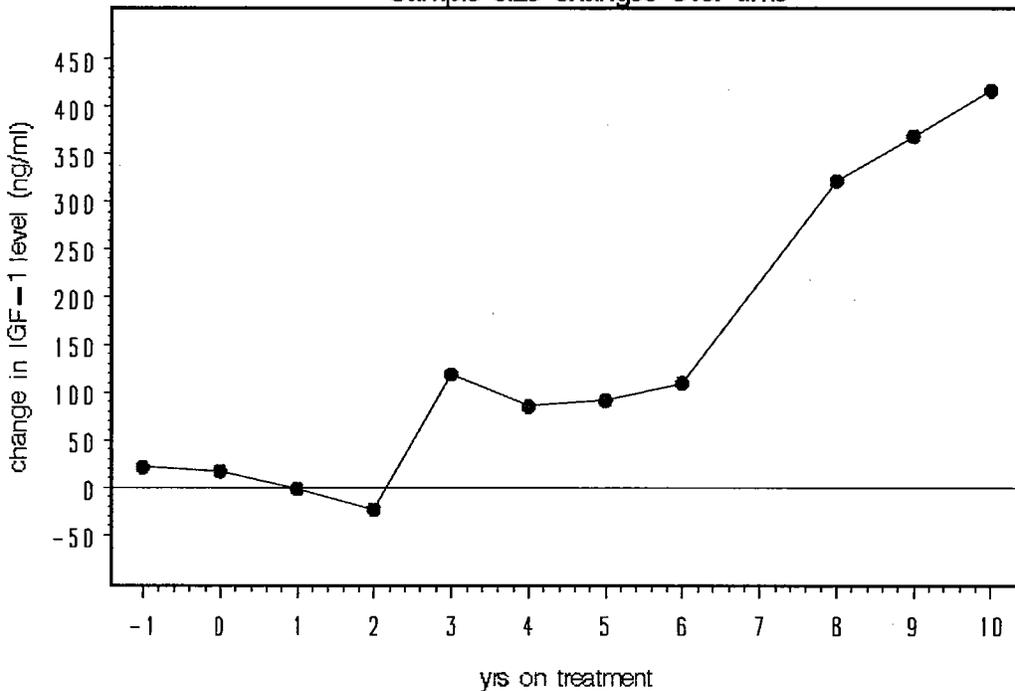
1 Years since initiation of IGF-1 treatment rounded to nearest whole year

2 Negative sign indicates one year prior to IGF-1 treatment

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Figure 4

med change in IGF1 (post-pre) by yrs of trt  
 Yrs rounded to nearest whole yr  
 Sample size changes over time



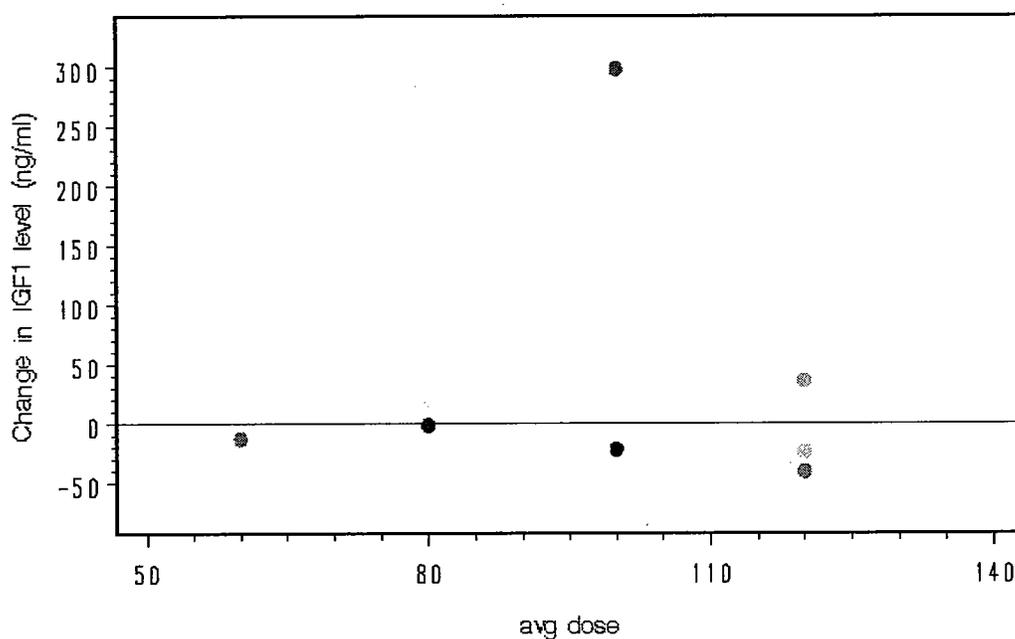
Most patients had multiple PK measurements across time. For the statistical analysis of changes (post minus pre-dose) in IGF-1 levels, the reviewer averaged changes within a patient before combining the data across patients in order to maintain the patient as the unit of analysis. Table 12 shows the reviewer's analysis results. Post-dose IGF-1 levels were significantly higher than pre-dose levels ( $p=.0002$ , signed rank test). The analysis averaged the results across time. However, the overall significant result was driven by IGF-1 increases in the group of patients with data at 3 and 4 years of treatment ( $n=11$ ). There was no evidence that IGF-1 levels were increased in patients sampled during the first 2 years of treatment ( $n=15$ ). It is left to clinical to judge whether treatment duration and related confounders such as age and dose explain these results.

Table 12. Reviewer's analysis of IGF-1 (ng/mL)

	# pts	Mean	Median	Min	Max
Pre-dose IGF-1	23	39	41	0	78
Change in IGF-1 from pre-dose	23	+73	+73	-39	+299
$p=.0002$ signed rank test					

To investigate more closely changes in IGF-1 levels at one year and the relationship with dose, Figure 5 depicts individual patient IGF-1 changes by dose (n=9). The Figure shows there was no dose response.

Figure 5  
Change in IGF1 (postdose—predose)  
1 yr of treatment (+/- 0.5 yrs)  
One data point per patient



In summary, median 2-hour post-dose IGF-1 levels were increased over pre-dose levels ( $p=.0002$  signed rank test). The increase was driven by a cohort of 11 patients treated for a minimum of 3 years. There was no evidence that IGF-1 levels were increased after one year of treatment based on data from a largely different cohort of 15 patients. Clinical judgment is needed to determine whether treatment duration and related confounders such as age and dose explain these results.

## Antibodies and height

Serial serum samples for anti-IGF-1 antibodies were assayed in Studies 206s, 375g, 632g and 671g in 23 patients over a mean duration of 4.4 years (range 1.5 to 6.6 yrs). Patients had a median of 8 samples (range 3 to 14). Twenty-two (22) subjects had antibody titer data during the first year of treatment. First-year antibodies are a reasonable but imperfect measure of the occurrence of antibodies in subsequent years as shown by the following table.

**Number of patients with antibodies**

Antibodies during the first year	Antibodies anytime after 1 <sup>st</sup> year	
	Yes	No
Yes	7	4
No	2	9

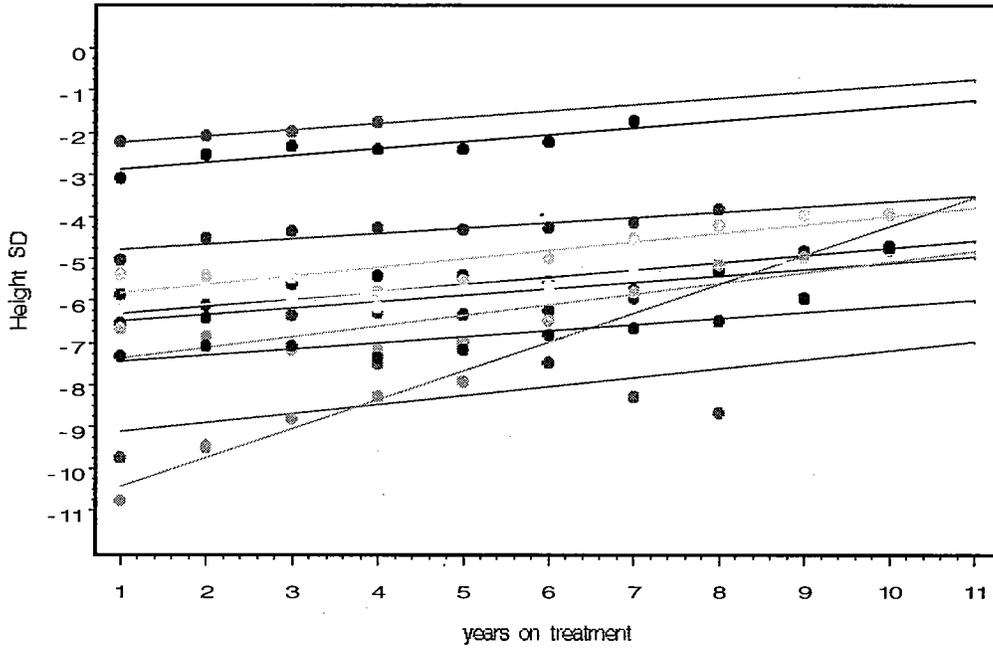
Eleven of 22 (50%) patients had positive titer at least once during the first year. Table 12 re-produces sponsor's table 11.14-1 showing no difference ( $p=.62$ ) in first-year height velocity for negative and positive titer patients.

**Table 12. First year results for subjects with and without antibodies to IGF-1**

	Subjects w/o antibodies (n=11)	Subjects w/ antibodies (n=11)
F/M	3/8	4/7
Baseline age (yrs) (range)	7.4 (1.7, 15.2)	6.3 (2.3, 13.5)
Ht velocity (cm/yr) (range)	7.3 (2.4, 12.8)	7.9 (5.3, 11.3)

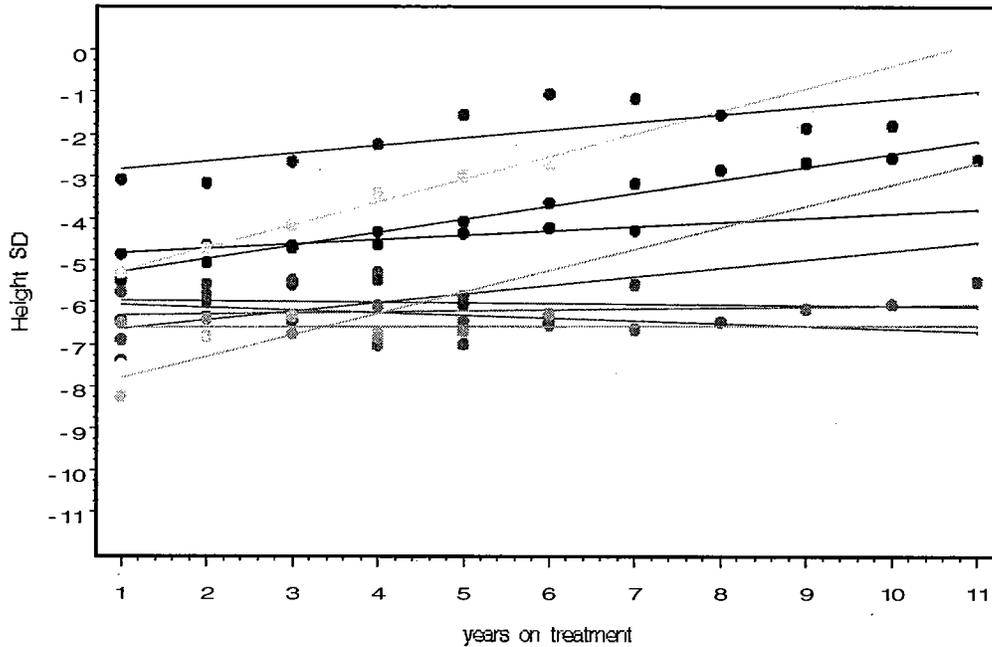
Due to the expected lag between the development of antibodies and potential effects on growth, this reviewer analyzed serial height SD scores for the 2 cohorts of patients defined by the sponsor. All height data collected on treatment were used in the analysis. Height SD was chosen as the endpoint for analysis rather than height velocity. SD scores adjust for age and gender which are variables that could potentially confound the interpretation of any observed differences over time between the cohorts. Figure 6 shows fitted regression lines, one line for each patient's height SD scores, for first-year antibody negative (first graph) and antibody positive (second graph) patients.

Figure 6  
Height SD score by 1st year titer (Yes/No)  
One regression line per patient  
titergr1=no



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Figure 6  
 Height SD score by 1st year titer (Yes/No)  
 One regression line per patient  
 titergr1=yes



Regression slopes from the graphs were compared statistically between the cohorts using a 2-sample Wilcoxon (nonparametric) test due to the non-normality of the distributions. The Wilcoxon was not statistically significant (Table 13,  $p=0.32$ ) indicating that patients with and without antibodies experienced similar rates of height change over time. However, three patients (#10905, 10909 and 18005) with positive antibodies had negative slopes whereas all patients without antibodies had positive slopes. Consequently the clinical course with respect to height was more variable for patients with positive antibodies during the first year.

**Table 13. Height SD scores: Reviewer's analysis of regression slopes**

Height SD	Subjects w/o antibodies (n=11)	Subjects w/ antibodies (n=11)
Mean slope (SD)	0.220 (0.160)	0.159 (0.215)
Median	0.164	0.103
Min, max	0.128, 0.689	-0.065, 0.540
P=0.32 (Wilcoxon)		

Results were similar for the analysis of height SD scores starting at two years comparing cohorts based on antibodies at any time during the first two years of treatment.

In summary, the presence or absence of antibodies to IGF-1 treatment during the first year was not associated with differences in rates of long-term height increases measured by height SD. The clinical course with respect to height was more variable for patients with positive antibodies during the first year.

### 3.2 Evaluation of Safety

#### Hypoglycemia

Table 14 re-produces the sponsor’s table 13.2.2.1-1 showing means for baseline measures of height SD, IGF-1 SD, age and prior history of hypoglycemia stratified by occurrence of hypoglycemia (Y/N) during the first year. The data differ from the sponsor’s data for prior history of hypoglycemia. The sponsor reported 18 patients with a history of hypoglycemia. this reviewer located only 14 such patients in the EDR (xmedhist.xpt). The result was still nominally significant ( $p=.037$ ) comparing numbers of patients with hypoglycemia by prior history status but not as significant as the sponsor’s result ( $p=.0018$ ).

**Table 14. Patients completing at least one year of mecaseimerin treatment who did or did not experience hypoglycemia**

	Patients w/o hypoglycemia (n=33)	Patients with hypoglycemia (n=28)	t-test or Fisher’s Exact
Mean baseline Height SD score	-6.2	-7.3	0.029
Mean baseline IGF-1 SD score	-4.5	-4.1	0.3118
Mean baseline age (yrs)	7.9	5.3	0.0051
# pts w/ prior history of hypoglycemia	4	10 <sup>1</sup>	0.037

<sup>1</sup>Sponsor reported 14 patients with hypoglycemia during the first year who had a prior history of hypoglycemia

As an exploratory analysis, this reviewer performed a stepwise logistic regression on the outcome variable of hypoglycemia (Y/N) starting with all the predictor variables in the Table plus baseline bone age. The alpha required for inclusion in the model at each step was set at 0.10, for exclusion 0.15. The final model eliminated all predictors except baseline age ( $p=.0014$ ) and height SD ( $p=.0027$ ). This analysis supports the sponsor’s contention that hypoglycemia occurred more often in younger and/or shorter patients.

## GFR

Glomerular filtration rate (GFR) is a measure of kidney function with low values indicating kidney dysfunction or failure. The sponsor measured GFR serially in 13 patients. Each patient had 6 measurements except patients 18009 and 18010 who had 5 measurements each. Measurements were taken over a mean of 3.3 years (range 2.6 to 3.7 yrs). The sponsor reported that GFR rose from initial (not necessarily baseline) to final GFR observations in 10 of 12 patients. This reviewer reanalyzed the GFR results using the raw data provided by the sponsor and submitted to the EDR. The raw data for initial and final observed GFR are shown in Table 15. GFR rose in 8 of 13 patients and declined in 5 patients.

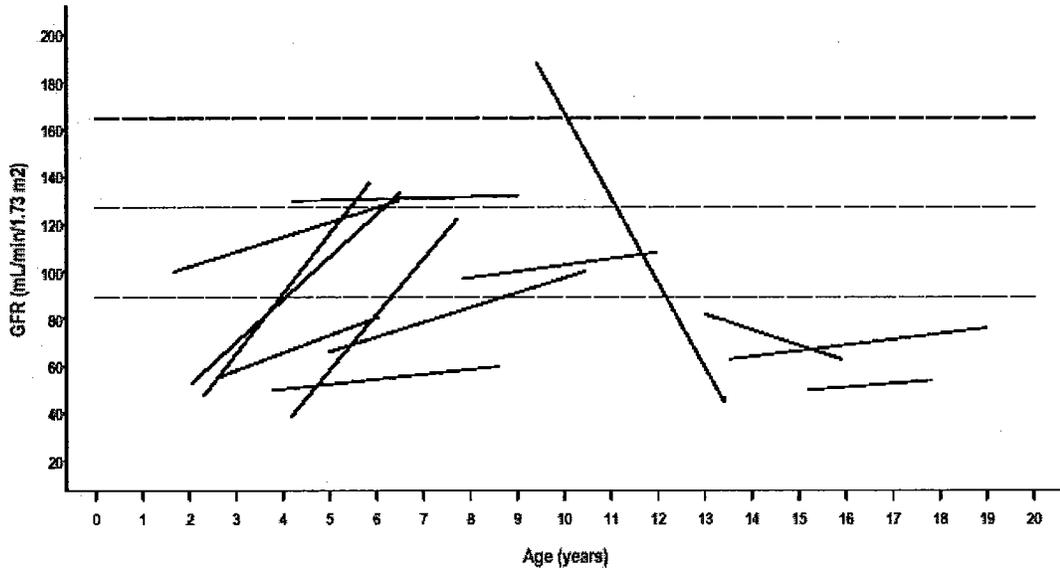
**Table 15. Initial and final observed GFR (mL/min/1.73m<sup>2</sup>)**

Patient	Initial GFR	Age (yr) at initial	Final GFR	Age (yr) at final	Change in GFR
18001	61	6.8	100	10.4	+39
18002	53	15.4	76	19.0	+23
18003	171	3.5	130	6.5	-41
18004	128	6.0	132	9.0	+4
18005	78	4.9	60	8.6	-18
18006	60	3.0	133	6.5	+73
18007	123	8.3	108	11.9	-15
18008	101	9.9	45	13.4	-56
18009	55	2.6	81	6.1	+26
18010	50	15.2	54	17.8	+4
18011	39	4.2	122	7.7	+83
18012	48	2.3	137	5.8	+89
18013	82	13.0	63	15.9	-19
<b>Mean</b>	<b>81</b>	<b>7.3</b>	<b>96</b>	<b>10.7</b>	<b>+15</b>
<b>Median</b>	<b>61</b>	<b>6.0</b>	<b>100</b>	<b>9.0</b>	<b>+4</b>

Sponsor's Figure 16.2.11.9 shows initial and final observed GFR by patient.

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Figure 16.2.11.9  
First and Last Observed GFR versus Age

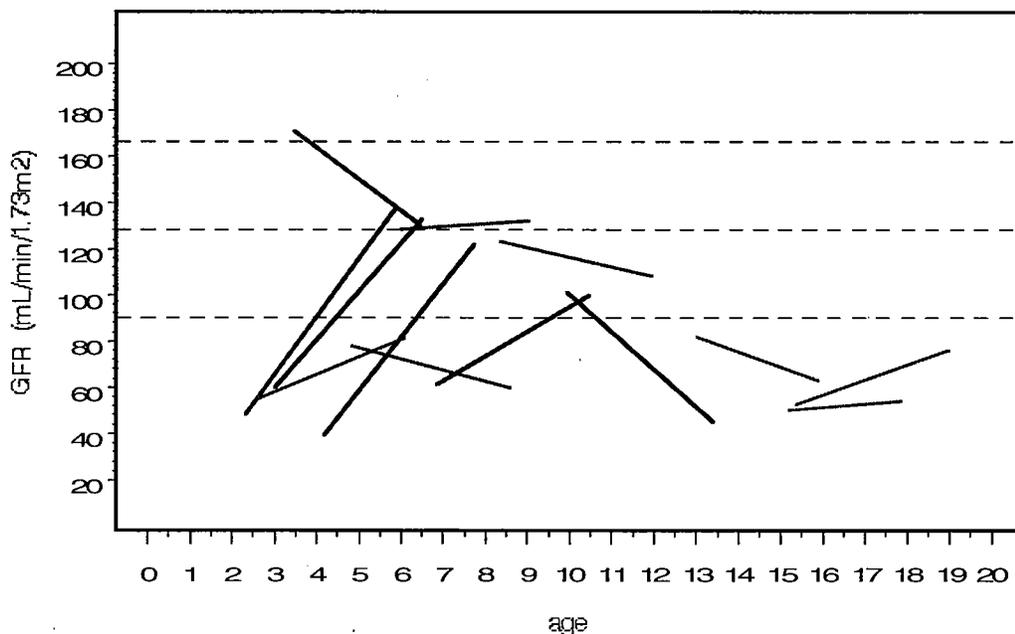


N = 13  
Source Data: studyrx,rspectst and vitals for Study f0375g  
s:\dat\tercica\nda\sas\testtg\_gfr\_23NOV2004 12:03

This reviewer's Figure 7 is similar in format to the sponsor's Figure 16.2.11.9 but is based on the data from Table 15. The horizontal reference lines approximate the reference lines in the sponsor's graph.

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On Original

Figure 6  
 First and last observed GFR by age  
 One line per patient



### Bone age

A safety concern was whether normalization of linear growth with mecaseimerin was associated with an undue acceleration of bone age indicating a potential risk of compromising final height. Since final height was achieved by only 3 patients, the analyses of bone age compare changes in bone age using the last measured bone age and the corresponding change in chronological age.

Bone age was evaluated approximately yearly. Table 16 shows changes in bone age at the last measurement for (1) patients with both a baseline (initial) bone age and a second bone age evaluation after at least one year of treatment (n=49) and (2) the population in (1) with results stratified by Lupron use prior to the last bone age evaluation. Lupron is used in some patients to delay puberty with the object of prolonging the growth period with the goal of additional growth. Lupron is known to decrease growth velocity and slow bone age advancement. Eight patients took Lupron prior to the last bone age measurement. Lupron exposure ranged from 4 to 51 months before the last bone age.

Bone age at baseline was significantly smaller than chronological age. The mean baseline bone age (4.3 yrs) was almost 3 years below the mean chronological age (7.1 yrs).

Bone age trended towards a significant increase relative to change in chronological age (5.3 yrs vs 4.9 yrs, p=.07). Counter-intuitively, the eight Lupron patients experienced greater numerical (non-significant) relative advances in bone age than non-Lupron patients.

**Table 16. Bone age results at last measurement**

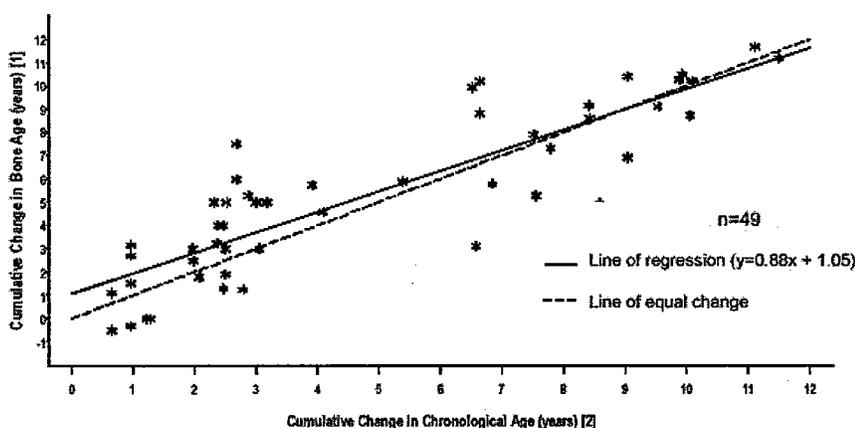
	Bone age (yrs)	Chronological age (yrs)
<b>All patients (n=49)</b>		
Mean at baseline <sup>1</sup>	4.26	7.10
Change from baseline (SD)	+5.34 (3.43)	+4.87 (3.37)
Difference (95% CI)	0.47 (-0.04, 0.98) p=.07	
<b>Patients without Lupron (n=41) <sup>2</sup></b>		
Mean at baseline <sup>1</sup>	3.69	6.32
Change from baseline (SD)	+5.10 (3.47)	+4.74 (3.27)
Difference (95% CI)	0.36 (-0.24, 0.96) p=.23	
<b>Patients with Lupron (n=8) <sup>2</sup></b>		
Mean at baseline <sup>1</sup>	7.21	11.10
Change from baseline (SD)	+6.57 (3.15)	+5.53 (4.01)
Difference (95% CI)	1.04 (0.25, 1.83)	

1 baseline bone evaluation

2 Prior to last bone age evaluation

The sponsor's Figure 11.9-1 shows the change in bone age ( $\Delta B$ ) at the last measurement versus the change in chronological change ( $\Delta C$ ) (n=49). The regression line equation was  $\Delta B = 0.88\Delta C + 1.05$  which seems to approximate the line of equal change. (The sponsor calls the two lines "similar".) However, one can also see there are two clusters of patients defined more or less by the median change in age, 3.1 years. The bone ages of patients with fewer years of treatment appear to advance to a greater degree relative to changes in age than patients treated for longer periods.

Figure 11.9-1: Cumulative Change in Bone Age versus Change in Chronological Age (Subjects Naïve to Mecasermin)



[1] Change from first bone age assessment to last bone age assessment  
 [2] Change in age from time of first bone age assessment to time of last bone age assessment

Table 17 shows bone age results by the median change in age, a rough surrogate for treatment duration. Patients below the median (consisting entirely of ongoing patients new to Study 1419) had a statistically greater change in bone age (2.8 years) compared to the change in chronological age (2.0 years) ( $p=.025$ ). On average, bone age advanced almost a year beyond the increase in chronological age, a 40% increase beyond the change in chronological age. The results for the subgroup were even more striking when excluding data from the two patients with negative changes in bone age ( $p=.009$ ) or all four patients with non-positive changes ( $p=.002$ ). Clearly these data require a careful interpretation since cohorts are defined (roughly) by duration of treatment and not by randomized groups.

Table 17. Bone age results at last measurement by median change in chronological age

Change in chronological age	Bone age (yrs)	Chron age (yrs)
<u>Below the median age change (n=25)</u>		
Mean at baseline	4.09	7.10
Change from baseline (SD)	+2.82 (2.08)	+2.02 (0.79)
Difference (95% CI)	0.80 (0.09, 1.51)	
	$p=.025$	
<u>Greater than the median age change (n=24)</u>		
Mean at baseline	4.44	7.11
Change from baseline (SD)	+7.97 (2.43)	+7.85 (2.23)
Difference (95% CI)	0.12 (-0.60, 0.85)	
	$p=.74$	

#### 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

##### 4.1 Gender, Race and Age

There were no statistical differences ( $p \geq 0.26$ ) in first year height velocity (Tables 18-20) or height velocity SD (not shown) between cohorts defined by sex, race or age. Females had numerically higher growth rates than males but received slightly larger average doses.

**Table 18. First year height velocity by gender**

	Males (n=35)	Females (n=23)	Diff
<u>Dose (<math>\mu\text{g}/\text{kg}</math>)</u>			
Mean (SD)	98 (26)	108 (20)	-10
Median	117	119	-2
<u>Height velocity (cm/yr)</u>			
Baseline mean (SD)	2.84 (1.59)	2.73 (2.17)	+0.10
Year 1 mean change from baseline (SD)	+4.89 (2.82)	+5.69 (2.26)	-0.80 p=0.26

**Table 19. First year height velocity by race**

	Caucasian (n=45)	Non- caucasian (n=13)	Diff
<u>Dose (<math>\mu\text{g}/\text{kg}</math>)</u>			
Mean (SD)	104 (24)	97 (25)	+7
Median	120	109	+11
<u>Height velocity (cm/yr)</u>			
Baseline mean (SD)	2.92 (1.93)	2.39 (1.42)	+0.53
Year 1 mean change from baseline (SD)	+5.47 (2.25)	+4.29 (3.60)	+1.18 p=0.28

**Table 20. First year height velocity by age category**

	Below med age (n=29)	Above med age (n=29)	Diff
<u>Dose (<math>\mu\text{g}/\text{kg}</math>)</u>			
Mean (SD)	101 (25)	104 (24)	-3
Median	119	119	0
<u>Height velocity (cm/yr)</u>			
Baseline mean (SD)	3.14 (2.13)	2.46 (1.42)	+0.68
Year 1 mean change from baseline (SD)	+4.93 (2.62)	+5.48 (2.64)	-0.55 p=0.43

## 4.2 Other Special/Subgroup Populations

### Subgroups defined by diagnosis

There were no statistical differences ( $p=0.70$ ) in first year height velocity (Table 21) or height velocity SD (not shown) between cohorts defined by diagnosis (Laron-type, other).

**Table 21. First year height velocity by Diagnosis**

	Laron-type (n=50)	Other (n=8)	Diff
<u>Dose (<math>\mu\text{g}/\text{kg}</math>)</u>			
Mean (SD)	103 (23)	.98 (30)	+5
Median	119	120	-1
<u>Height velocity (cm/yr)</u>			
Baseline mean (SD)	2.91 (1.85)	2.10 (1.61)	+0.81
Year 1 mean change from baseline (SD)	+5.15 (2.57)	+5.55 (3.12)	-0.40
			$p=0.70$

### Subgroups defined by Study 671g enrollment (Y/N)

Patients enrolled through Study 671g ( $n=23$ ) underwent a “stricter protocol” than patients enrolled subsequently. The sponsor claimed that baseline and Year 1, 2 and 3 height velocities were “similar” in the 2 cohorts (June 20, 2005 submission). The sponsor did not evaluate changes from baseline. This reviewer found a significant difference ( $p=0.021$ ) for first year height velocity change from baseline and a statistical trend ( $p=0.105$ ) for height velocity SD change from baseline (Table 22).

**Table 22. First year height velocity by Study 671g enrollment (Y/N)**

	Study 0671g (n=23)	Study 1419 only (n=35)	Diff
<u>Dose (<math>\mu\text{g}/\text{kg}</math>)</u>			
Mean (SD)	89 (24)	111 (20)	-22
Median	91	120	-29
<u>Height velocity (cm/yr)</u>			
Baseline mean (SD)	3.25 (1.97)	2.50 (1.69)	+0.75
Year 1 mean change from baseline (SD)	+4.24 (2.49)	+5.84 (2.54)	-1.61
			$p=0.021$
<u>Height velocity SD</u>			
Baseline mean (SD)	-2.75 (1.73)	-3.64 (1.57)	+0.89
Year 1 mean change from baseline (SD)	+4.36 (3.43)	+5.71 (2.76)	-1.35
			$p=0.105$

## APPENDICES

### Appendix 1: By-center\_demographics and baseline characteristics for numeric variables (patients with $\geq$ one year of treatment)

#### University of North Carolina (n=48)

	N	Mean	SD	Min	Max
Age (years)	48	6.7	3.5	1.7	15.2
Height (cm)	48	85.7	15.2	63.2	133.1
Height SD Score	48	-6.6	1.6	-10.7	-3.2
Pre-Treatment Height Velocity (cm/yr)	45	2.7	1.7	0.0	7.6
Pre-Treatment Height Velocity SD Score	45	-3.5	1.6	-6.6	-0.5
Baseline IGF-1 (ng/mL)	43	16.1	13.4	0.2	72.0
Baseline IGF-1 SD Score	43	-4.6	1.5	-9.5	-2.0
Weight (kg)	46	13.1	6.3	6.5	35.0
BMI (kg/m <sup>2</sup> )	46	16.7	2.5	12.8	24.6
BMI SD Score	45	0.0	1.1	-3.1	2.2
Bone Age (years)	44	4.1	2.8	0.3	12.3
Maximum IGF-1 Concentration from IGF-1 Gen Test (ng/mL)	31	19.6	20.4	0.5	81.0
Maximum IGF-1 SD Score from IGF-1 Gen Test	31	-4.7	1.9	-8.9	-0.5
Maximum Growth Hormone Concentration (ng/mL)	44	52.3	42.4	0.5	209.0

#### Children's Hospital Medical Center Cincinnati (n=13)

	N	Mean	SD	Min	Max
Age (years)	13	6.5	4.8	1.7	15.2
Height (cm)	13	80.1	15.6	61.2	111.4
Height SD Score	13	-7.0	2.5	-12.1	-2.8
Pre-Treatment Height Velocity (cm/yr)	13	3.2	2.1	0.5	7.7
Pre-Treatment Height Velocity SD Score	13	-2.7	2.0	-5.2	0.9
Baseline IGF-1 (ng/mL)	13	39.7	29.2	5.0	82.1
Baseline IGF-1 SD Score	13	-3.3	1.7	-5.6	-0.7
Weight (kg)	13	10.5	4.6	5.8	21.5
BMI (kg/m <sup>2</sup> )	13	15.8	2.4	12.9	22.5
BMI SD Score	12	-0.9	1.2	-2.8	1.1
Bone Age (years)	13	4.3	3.1	0.8	9.9
Maximum IGF-1 Concentration from IGF-1 Gen Test (ng/mL)	5	36.0	44.7	6.0	115.0
Maximum IGF-1 SD Score from IGF-1 Gen Test	5	-3.5	1.8	-5.2	-0.6
Maximum Growth Hormone Concentration (ng/mL)	11	69.4	59.3	0.5	190.0

## Appendix 2. Annualized height velocity SD by number of years treated

	Pre-dose	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
<b>Subjects Completing 1 Year</b>									
N	58	58							
Mean (SD)	3.3 (1.7)	1.9 (3.0)							
Median	-3.3	1.7							
Min, Max	-6.6, 0.9	-4.4, 15.4							
Mean (SD) for change from pre-dose	N/A	5.2 (3.1)							
P-value for change from pre-dose [1]	N/A	<0.0001							
95% CI for change from pre-dose	N/A	(4.4, 6.0)							
<b>Subjects Completing 2 Years</b>									
N	47	47	47						
Mean (SD)	-3.4 (1.6)	1.8 (2.4)	-0.2 (1.6)						
Median	-3.3	1.8	-0.3						
Min, Max	-6.6, 0.9	-3.3, 6.5	-4.8, 3.2						
Mean (SD) for change from pre-dose	N/A	5.1 (2.8)	3.1 (2.3)						
P-value for change from pre-dose [1]	N/A	<0.0001	<0.0001						
95% CI for change from pre-dose	N/A	(4.3, 5.9)	(2.5, 3.8)						
<b>Subjects Completing 3 Years</b>									
N	37	37	37	37					
Mean (SD)	-3.1 (1.6)	1.6 (2.6)	-0.2 (1.4)	-0.2 (2.0)					
Median	-2.9	1.2	-0.3	-0.4					
Min, Max	-6.6, 0.9	-3.3, 6.5	-3.5, 3.1	-4.1, 5.5					
Mean (SD) for change from pre-dose	N/A	4.7 (2.9)	2.9 (2.0)	2.9 (2.3)					
P-value for change from pre-dose [1]	N/A	<0.0001	<0.0001	<0.0001					
95% CI for change from pre-dose	N/A	(3.8, 5.7)	(2.2, 3.5)	(2.1, 3.7)					
<b>Subjects Completing 4 Years</b>									
N	22	22	22	22	22				
Mean (SD)	-2.9 (1.6)	1.0 (2.7)	-0.4 (1.5)	-0.8 (1.6)	-0.7 (2.1)				
Median	-2.9	0.7	-0.4	-1.0	-1.0				
Min, Max	-5.9, 0.9	-3.3, 6.5	-2.5, 3.1	-4.1, 2.1	-4.4, 3.9				
Mean (SD) for change from pre-dose	N/A	3.9 (2.6)	2.5 (2.0)	2.1 (1.9)	2.2 (2.2)				
P-value for change from pre-dose [1]	N/A	<0.0001	<0.0001	<0.0001	0.0001				
95% CI for change from pre-dose	N/A	(2.7, 5.0)	(1.6, 3.4)	(1.3, 3.0)	(1.2, 3.1)				
<b>Subjects Completing 5 Years</b>									
N	19	19	19	19	19	19			
Mean (SD)	3.1 (1.6)	1.0 (2.8)	-0.4 (1.6)	-0.9 (1.7)	-1.1 (1.9)	-0.6 (2.1)			
Median	-2.9	0.9	-0.6	-1.1	-1.4	-0.6			
Min, Max	-5.9, 0.9	-3.3, 6.5	-2.5, 3.1	-4.1, 2.1	-4.4, 3.2	-3.8, 5.3			
Mean (SD) for change from pre-dose	N/A	4.1 (2.7)	2.6 (2.1)	2.2 (2.0)	2.0 (2.2)	2.5 (2.2)			
P-value for change from pre-dose [1]	N/A	<0.0001	<0.0001	0.0002	0.0009	0.0001			
95% CI for change from pre-dose	N/A	(2.8, 5.4)	(1.6, 3.7)	(1.2, 3.1)	(1.0, 3.1)	(1.4, 3.6)			
<b>Subjects Completing 6 Years</b>									
N	18	18	18	18	18	18	18		
Mean (SD)	3.1 (1.7)	1.0 (2.9)	-0.5 (1.6)	-1.0 (1.7)	-1.2 (1.8)	-0.9 (1.6)	-0.4 (1.4)		
Median	-3.1	1.0	-0.9	-1.1	-1.5	-0.7	-0.6		
Min, Max	-5.9, 0.9	-3.3, 6.5	-2.5, 3.1	-4.1, 2.1	-4.4, 3.2	-3.8, 2.2	-3.1, 2.0		
Mean (SD) for change from pre-dose	N/A	4.1 (2.7)	2.6 (2.2)	2.1 (2.0)	1.9 (2.2)	2.2 (1.8)	2.7 (1.7)		
P-value for change from pre-dose [1]	N/A	<0.0001	<0.0001	0.0004	0.0020	<0.0001	<0.0001		
95% CI for change from pre-dose	N/A	(2.8, 5.5)	(1.5, 3.7)	(1.1, 3.1)	(0.8, 3.0)	(1.3, 3.1)	(1.9, 3.5)		
<b>Subjects Completing 7 Years</b>									
N	15	15	15	15	15	15	15	15	
Mean (SD)	2.9 (1.6)	0.6 (2.8)	-0.7 (1.5)	-1.2 (1.6)	-1.6 (1.6)	-1.1 (1.7)	-0.5 (1.5)	-0.4 (1.9)	
Median	-2.9	0.9	-1.1	-1.2	-1.6	-1.0	-0.8	-0.1	
Min, Max	-5.2, 0.9	-3.3, 6.5	-2.5, 2.9	-4.1, 2.1	-4.4, 1.2	-3.8, 2.2	-3.1, 2.0	-3.9, 3.2	
Mean (SD) for change from pre-dose	N/A	3.5 (2.4)	2.2 (1.9)	1.7 (1.8)	1.3 (1.6)	1.8 (1.4)	2.4 (1.4)	2.5 (2.1)	
P-value for change from pre-dose [1]	N/A	<0.0001	0.0006	0.0024	0.0067	0.0003	<0.0001	0.0003	
95% CI for change from pre-dose	N/A	(2.2, 4.8)	(1.1, 3.2)	(0.7, 2.7)	(0.4, 2.2)	(1.0, 2.6)	(1.6, 3.2)	(1.4, 3.7)	
<b>Subjects Completing 8 Years</b>									
N	11	11	11	11	11	11	11	11	11
Mean (SD)	3.1 (1.8)	-0.6 (2.0)	-1.4 (0.8)	-1.1 (1.6)	-1.6 (1.6)	-1.2 (1.9)	-0.7 (1.6)	-0.9 (1.6)	-0.4 (1.9)
Median	-3.3	-1.0	-1.6	-1.2	-1.7	-1.9	-1.0	-0.2	-0.4
Min, Max	-5.2, 0.9	-3.3, 3.1	-2.5, -0.2	-3.5, 2.1	-4.4, 1.2	-3.8, 2.2	-3.1, 2.0	-3.9, 1.5	-2.7, 4.3
Mean (SD) for change from pre-dose	N/A	2.5 (1.8)	1.7 (2.0)	2.0 (1.8)	1.5 (1.7)	1.9 (1.6)	2.4 (1.7)	2.2 (2.3)	2.7 (2.8)
P-value for change from pre-dose [1]	N/A	0.0010	0.0173	0.0053	0.0136	0.0030	0.0008	0.0093	0.0086
95% CI for change from pre-dose	N/A	(1.3, 3.7)	(0.4, 3.0)	(0.7, 3.2)	(0.4, 2.6)	(0.8, 2.9)	(1.3, 3.5)	(0.7, 3.7)	(0.9, 4.6)

[1] p-values computed using paired-t test

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Concur with review.



U.S. Department of Health and Human Services  
Food and Drug Administration

Center for Drug Evaluation and Research  
Office of Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

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### CARCINOGENICITY STUDIES

**NDA/Serial Number:** 21839/N000

**Drug Name:** Increlex

**Applicant:** Tercica, Inc.

**Biometrics Division:** Biometrics Division 2

**Statistical Reviewer:** Moh-Jee Ng, M.S. (HFS-715)

**Concurring Reviewers:** Karl Lin, Ph.D. (HFS-715)

**Documents Reviewed** \\CDSESUB1\N21839\N\_000\2005-02-24

**Medical Division:** Division of Metabolic and Endocrine Drug Products

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**Project Manager:** Enid M.Galliers

**Keywords:** NDA review, carcinogenicity

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## Executive Summary

In the 2-year rat study, there were significant positive trends and statistically significant differences in survival distributions among the treatment groups in both males and females. Significantly positive dose-response relationships in incidence rate of carcinoma in mammary, keratoacanthoma in skin in males were detected. The positive trend in pheochromocytoma in adrenal medulla was significant in both males and females.

## Introduction

The objective of this review is to evaluate the oncogenic potential of rhIGF-I (recombinant human Insulin-like Growth Factor-I) given to rats by subcutaneous injection daily for up to 84 weeks. There were one vehicle control group and four treated groups known as low, med 1, med 2 and high. The dose levels for the treatment groups were 0, 0.25, 1.0, 4.0 and 10.0 mg/kg/day. There were 75 animals of each sex in each treatment group. Animals in high dose group were terminated during week 84. All remaining surviving animals were necropsied at week 99 for males and at week 105 for females. The study design is summarized in Table 1.

Table 1: Summary of Study Designs

Species	Rat
Strain	\ CD@ (SD)BR VAF/Plus®
Route of Administration	Subcutaneous injection
Frequency of Drug Administration	Daily
Dose Unit	mg/kg/day
Dose Level	0 (Vehicle Control 1) 0.25 ( Low) 1.0 (Mid 1) 4.0 (Mid 2) 10.0 (High)
Number of Animals/sex/per treatment group	75 males/group 75 females/group
Length of Study	99 weeks for males 105 weeks for females

## Reviewer's Evaluation of Carcinogenicity Study

This reviewer performed independent analyses on the survival and tumor data submitted by the sponsor, using the programs written by Dr. Ted Guo of Division of Biostatistics II. The primary statistical methods used were described by Peto *et al.* (1980), and Lin and Ali (1994). These methods adjust differences in animal mortality and take the fatal or incidental context of observation of the tumor into consideration. The intervals used for the adjustment of mortality were 0-50, 51-78, 79-83, 84-99 for males or 0-50, 51-78, 79-83, 84-105 weeks for females, and the terminal sacrifice was week 99 for males and week 105 for females. The actual doses were used as weights in the analyses.

The statistical analyses of the tumor data consisted of two parts, namely, the survival data analysis and the tumor data analysis. The survival data analysis was: 1) to examine the differences in survival distributions among the treatment groups (homogeneity test); and 2) to determine if there is a positive trend in the proportion of deaths with respect to the dose levels (Trend test). Two statistical tests were used in the survival data analysis: the Cox test and the generalized Kruskal-Wallis test. The theoretical background of these tests was described by Lin and Ali (1994) and Thomas *et al* (1977).

The tumor data analysis was to determine if there is a positive trend in the proportions of a selected tumor type in a selected organ/tissue with respect to the dose levels. The tumors were classified as either fatal or incidental, according to Peto *et al* (1980). The reviewer applied the death-rate method to fatal tumors and the prevalence method to incidental tumors. For tumors that caused death for some, but not for all, animals, a combined test was performed.

A rule for adjusting the effect of multiple testings proposed by Haseman (1983) can be used to adjust for the effect of multiple testings in pairwise comparisons. Haseman's rule says that, for pairwise comparisons, rare tumors should be tested at 0.05 level of significance and common tumors should be tested at 0.01 level of significance. A similar rule proposed by the Office of Biostatistics, CDER/FDA for trend tests was used in this review. The rule states that in order to keep the overall false-positive rate at the nominal level of approximately 0.1, tumor types with spontaneous tumor rates of 1% or less (rare tumors) should be tested at 0.025 significance level, otherwise (common tumors) at 0.005 significance level (Lin and Rahman, 1998).

## **Analysis of Male Rats**

### **Survival Data Analysis**

The mortality analysis determines whether the dose-mortality trend is statistically significant. A positive result indicates that mortality increases as the dose level increases.

- Table 2 includes the number of animals at risk, the number of deaths, the cumulative percentage of survival by treatment and age group, and the cumulative percentage of deaths by treatment and age group. The time interval "FINAL KILL" represents the terminal-sacrifice interval.
- Figure 1 presents the plot of Kaplan-Meier estimates of the survival distributions of the treatment groups of male rats.
- Table 3 presents results of test for dose-mortality trend for males using the methods described in the paper "Trend and homogeneity analysis of proportions and life table data" version 2.1, by Donald G. Thomas, National Cancer Institute.

Table 2: Analysis of Mortality Data for Male Rats by Treatment and Time

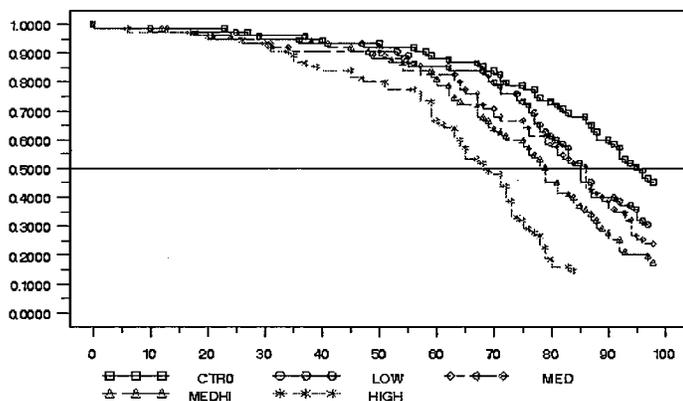
Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTRO	0-50	75	5	70	93.3	6.7
	51-78	70	14	56	74.7	25.3
	79-83	56	4	52	69.3	30.7
	FINALKILL 84-99	52	52	0		
LOW	0-50	75	6	69	92.0	8.0
	51-78	69	20	49	65.3	34.7
	79-83	49	6	43	57.3	42.7
	FINALKILL 84-99	43	43	0		
MED	0-50	75	7	68	90.7	9.3
	51-78	68	20	48	64.0	36.0
	79-83	48	8	40	53.3	46.7
	FINALKILL 84-99	40	40	0		
MEDHI	0-50	75	8	67	89.3	10.7
	51-78	67	27	40	53.3	46.7
	79-83	40	9	31	41.3	58.7
	FINALKILL 84-99	31	31	0		
HIGH	0-50	75	14	61	81.3	18.7
	51-78	61	41	20	26.7	73.3
	79-83	20	8	12	16.0	84.0
	FINALKILL 84-99	12	12	0		

Source data: dataset received on 2/24/2005, analysis data R4M21839

**Reviewer's comment on mortality data for male rats by treatment and Time:**

- The cumulative survival percentages at the end of the 79-83 week interval were 69%, 57%, 53%, 41% and 16% for the control group, low dose, med 1 dose, med 2 dose, and high dose group, respectively. Based on Haseman's (1984) rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be considered as a sufficient number of animals under an adequate exposure. The survivals between week 79 and week 83 for the high dose group was 16%. As noted previously 75 animals were used for each sex/group. It appears that the proportion of survival between week 79 and week 83 is not sufficient to provide adequate exposure at risk of late-developed tumors for the high dose group animals. Only 12 males of high dose group were still alive at week 83.

Figure 1: Kaplan-Meier Survival Functions for Male Rats



Source data: dataset received on 2/24/2005, analysis data R421839

Table 3: Analysis of Dose-Mortality Trend for Male Rats

	Method			
	Cox		Kruskal-Wallis	
	Statistic s	P- Value	Statistic s	P- Value
Time-Adjusted Trend Test				
Depart from Trend	3.6880	0.2972	2.8457	0.4160
Dose-Mortality Trend	63.7728	0.0000	56.0822	0.0000
Homogeneity	67.4608	0.0000	58.9279	0.0000

Source data: dataset received on 2/24/2005, analysis data R1M21839.  
Shaded areas showed statistically significant at 0.05 level.

#### Reviewer's comment on dose-mortality trend for male rats:

The dose-mortality trend was statistically significant using the Cox test and the Kruskal-Wallis test.

## Tumor Data Analysis

The tumor data analysis determines whether the positive linear trend in tumor incidence is statistically significant.

Table 4 lists the incidence rates of tumors with p-values < 0.05 in testing positive linear dose-tumor trends. The resulting p-values are compared against the p-value cutoff points set by the FDA procedures to determine if a positive trend is statistically significant. The check mark  indicates statistically significant test results, based on the decision rule of FDA CDER Divisions of Biometrics.

Table 4: Report of P-values &lt; 0.05 for Test Positive Linear Dose-Tumor Trends in Male Rats

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	MEDHI	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
LI	LIVER	480	B-ADENOMA, HEPATOCELLU	1	0	0	1	1	0.0725 *	0.0308
MA	ADRENAL, MEDULLA	135	B-PHEOCHROMOCYTOMA	10	12	16	25	18	0.0004 * (!)	0.0003
MM	MAMMARY, MALE	322	M-CARCINOMA	0	1	0	0	4	0.0006** (!)	0.0003
PC	CAVITY, ABDOM	196	M-SCHWANNOMA	0	0	0	0	1	0.0625 *	0.0007
SK	SKIN	177	B-KERATOACANTHOMA	1	4	3	9	18	0.0000 ** (!)	0.0000
SP	SPLEEN	197	M-SARCOMA, UNDIFFERENT	0	0	0	0	1	0.1629 *	0.0269
SP	SPLEEN	516	M-HEMANGIOSARCOMA	1	0	0	0	1	0.1306 *	0.0489
SV	SEMINAL VESICLES	463	M-CARCINOMA	0	0	0	1	1	0.0278 *	0.0032

Source data: dataset received on 2/24/2005, analysis data R1M21839

\*: using Exact p-value, since the overall tumor type is either fatal or incidental with spontaneous tumor rates of more than 1%, it should be tested at 0.005 significant level

\*\* : using Exact p-value, since the overall tumor type is incidental with spontaneous tumor rates of less than 1%, it should be tested at 0.025 significant level

This reviewer's counts of keratoacanthoma skin tumor bearing animals (1, 4, 3, 9, and 18 for the five treatment groups) are not consistent with the sponsor results (1, 4, 3, 11, and 19).

#### Reviewer's comment on testing positive linear dose-tumor trends in male rats:

- Significantly positive dose-response relationships in incidence rate in pheochromocytoma in adrenal medulla, carcinoma in mammary, and keratoacanthoma in skin were detected for males.

This reviewer performed an additional statistical analysis excluding the high dose group because the concern of the drastically reduced survival of the group. There were significant positive linear trends in incidence rate in pheochromocytoma in adrenal medulla, and in keratoacanthoma in skin (see Table 4). However, no significant in incidence rate in carcinoma in skin in males was detected.

## Analysis of Female Rats

### Survival Data Analysis

Survival data analyses determine whether the dose-mortality trend is statistically significant. A positive result indicates that mortality increases as the dose level increases.

- Table 5 includes the numbers of animals at risk, the number of deaths, the cumulative percentages of survival by treatment and age group, and the cumulative percentages of deaths by treatment and age group. The time interval "FINAL KILL" represents the terminal-sacrifice interval.

- Figure 2 presents the plot of Kaplan-Meier estimates of the survival distributions of the treatment groups of male rats.
- Table 6 presents results of test for dose-mortality trend for males using the methods described in the paper "Trend and homogeneity analysis of proportions and life table data " version 2.1, by Donald G. Thomas, National Cancer Institute.

Table 5: Analysis of Mortality Data for Female Rats by Treatment and Time

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR0	0-50	75	3	72	96.0	4.0
	51-78	72	22	50	66.7	33.3
	79-83	50	5	45	60.0	40.0
	FINALKILL 84-105	45	45	0		
LOW	0-50	75	1	74	98.7	1.3
	51-78	74	18	56	74.7	25.3
	79-83	56	5	51	68.0	32.0
	FINALKILL 84-105	51	51	0		
MED	0-50	75	3	72	96.0	4.0
	51-78	72	22	50	66.7	33.3
	79-83	50	9	41	54.7	45.3
	FINALKILL 84-105	41	41	0		
MEDHI	0-50	75	3	72	96.0	4.0
	51-78	72	35	37	49.3	50.7
	79-83	37	8	29	38.7	61.3
	FINALKILL 84-105	29	29	0		
HIGH	0-50	75	9	66	88.0	12.0
	51-78	66	42	24	32.0	68.0
	79-83	24	13	11	14.7	85.3
	FINALKILL 84-105	11	11	0		

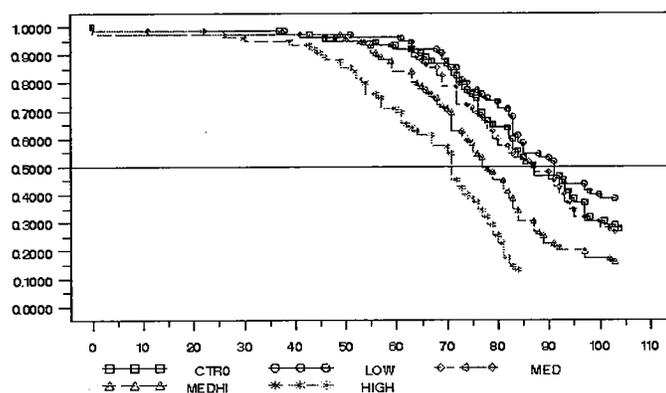
Source data: dataset received on 2/24/2005, analysis data R1F21839

**Reviewer's comment on mortality data for female rats by treatment and time:**

- The cumulative survival percentages at week79-83 were 60%, 68%, 55%, 39% and 15% for the control group, low dose, med 1 dose, med 2 dose, and high dose group, respectively. Based on Haseman's (1984) rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be considered as a sufficient number of animals under an adequate exposure. The survival percentage between week 79 and week 83 for the high dose group was 15%. As noted previously 75

animals were used for each sex/group. It appears that the proportion of survival between week 79 and week 83 is not sufficient to provide adequate exposure at risk of late-developed tumors for high dose group animals. Only eleven females of high dose group were still alive at week 83.

Figure 2: Kaplan-Meier Survival Functions for Female Rats



Source data: dataset received on 2/24/2005, analysis data R1F21827

Table 6: Analysis of Dose-Mortality Trend for Female Rats

	Method			
	Cox		Kruskal-Wallis	
	Statistic s	P-Value	Statistic s	P-Value
Time-Adjusted Trend Test				
Depart from Trend	1.8727	0.5992	1.1145	0.7736
Dose-Mortality Trend	68.5040	0.0000	68.7046	0.0000
Homogeneity	70.3767	0.0000	69.8191	0.0000

Source data: dataset received on 2/24/2005, analysis data R1F21839.  
Shaded area showed statistically significant at 0.05 level.

#### Reviewer's comment on dose-mortality trend for female rats:

The dose-mortality trend was statistically significant using the Cox test and the Kruskal-Wallis test.

### Tumor Data Analysis

The tumor data analysis determines whether the positive linear trend in tumor incidence is

statistically significant.

Table 7 lists the incidence rates of tumors with p-values < 0.05 for testing positive linear dose-tumor trends. The p-values are compared against the p-values cutoff point set by the FDA procedures to determine if a positive trend is statistically significant. The check mark (☑) indicates statistically significant test results, based on the decision rule of FDA CDER Divisions of Biometrics.

**Table 7: Report of P-values < 0.05 for Test Positive Linear Dose-Tumor Trends in Female Rats**

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	MEDHI	HIGH	P-Value (Monte Carlo)	P-Value (Asymptotic Method)
MA	ADRENAL, MEDULLA	120	B-PHEOCHROMOCYTOMA	1	6	6	8	13	0.0000 ☑	0.0000
PA	PANCREAS	473	B-ADENOMA, ACINAR CELL	0	0	0	0	1	0.0625 *	0.0010
PI	PITUITARY	10	B-ADENOMA	62	63	61	58	43	0.0021	0.0013 (☑)
SM	MUSCLE, SKELETAL	112	M-UNDIFFERENTIATED SARCOMA	0	0	0	0	1	0.1769	0.0318
ST	STOMACH, GL	323	M-LEIOMYOSARCOMA	0	0	0	0	1	0.1464	0.0190

Source data: dataset received on 2/24/2005, analysis data R1F21839

\*: using Monte Carlo p-value, since the overall tumor type is incidental with spontaneous tumor rates of less than 1%, it should be tested at 0.025 significant level

\*\*: using Exact p-value, since the overall tumor type is incidental with spontaneous tumor rates of more than 1%, it should be tested at 0.005 significant level

\*\*\*: using Asymptotic p-value, since the overall tumor type is both fatal and incidental with spontaneous tumor rates of more than 1%, it should be tested at 0.005 significant level

**Reviewer's comment on testing positive linear dose-tumor trends in male rats:**

- Significantly positive dose-response relationships in incidence rate in pheochromocytoma in adrenal medulla was detected in females.

This reviewer performed an additional statistical analysis excluding the high dose group because the concern of the drastically reduced survival of the group. No significant positive linear trend in incidence rate in any type of tumor was observed when the high dose group in females was excluded (see Table 8).

**Table 8: Report on Test for Positive linear Trends excluding of high dose group of Combined Tumor in Female Rats**

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	MEDHI	P-Value (Monte Carlo)	P-Value (Asymptotic Method)
LI	LIVER	202	B-ADENOMA, HEPATOCELLULAR	0	0	0	2	0.0525	0.0114
MA	ADRENAL, MEDULLA	120	B-PHEOCHROMOCYTOMA	1	6	6	8	0.0213	0.0192
MA	ADRENAL, MEDULLA	466	M-MALIGNANT PHEOCHROMOCYTOMA	0	0	0	1	0.1762	0.0389
MF	MAMMARY, FEMALE	29	B-FIBROADENOMA	22	35	29	33	0.0234	0.0265

MF	MAMMARY, FEMALE	346	B-MYOEPITHELIOMA	0	0	0	1	0.1794	0.0405
PI	PITUITARY	10	B-ADENOMA	62	63	61	58	0.0438	0.0416
TY	THYROID	126	M-CARCINOMA, FOLLICULAR CELL	0	1	1	2	0.0571	0.0488

Source data: dataset received on 2/24/2005, analysis data R1F21839

## Conclusion

In the 2-year rat study, there were significant positive trends and statistically significant differences in survival distributions among the treatment groups in both males and females. Significantly positive dose-response relationships in incidence rate of carcinoma in mammary, of keratoacanthoma in skin in males were detected. The trend in pheochromocytoma in adrenal medulla was significant in both males and females.

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## Appendices

Appendix 1: Report on Test for Positive Linear Dose-Tumor Trends in Male Rats

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	MEDHI	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
AC	ADRENAL, CORTEX	260	B-ADENOMA	1	1	0	1	2	0.2031	0.1909
AC	ADRENAL, CORTEX	352	M-CARCINOMA	1	0	0	0	0	1.0000	0.8083
BR	BRAIN	475	M-ASTROCYTOMA	0	0	2	0	0	0.4119	0.6403
BR	BRAIN	483	M-MALIGNANT GRANULAR C	1	0	0	0	0	1.0000	0.8482
BR	BRAIN	515	B-GRANULAR CELL TUMOR	2	0	0	0	1	0.1948	0.1604
BR	BRAIN	97	M-OLIGODENDROGLIOMA	0	1	0	0	0	0.7872	0.8027
CA	CALVARIUM/SKULL	522	B-OSTEOMA	1	0	0	0	0	1.0000	0.8988
CO	COLON	458	M-CARCINOMA	0	1	0	0	0	0.7079	0.7639
HN	HEMATO NEOPLASIA	307	M-LEUKEMIA, LARGE GRAN	0	0	0	1	0	0.2640	0.2605
HN	HEMATO NEOPLASIA	339	M-LEUKEMIA, GRANULOCYT	0	0	1	1	0	0.3972	0.5489
HN	HEMATO NEOPLASIA	363	M-HISTIOCYTIC SARCOMA	0	3	0	1	0	0.6475	0.7304
HN	HEMATO NEOPLASIA	365	M-MALIGNANT FIBROUS HI	2	1	1	0	0	0.9736	0.9498
HN	HEMATO NEOPLASIA	51	M-LYMPHOMA	2	3	1	3	0	0.8314	0.8450
HT	HEART	413	B-ATRIOCAVAL MESOTHELI	1	0	0	1	1	0.1843	0.1533
IS	INJECTION SITE	297	M-FIBROSARCOMA	1	0	1	2	0	0.5034	0.5055
IS	INJECTION SITE	395	B-ADENOMA, BASAL CELL	0	0	0	0	1	0.3361	0.1138
IS	INJECTION SITE	409	B-KERATOACANTHOMA	0	0	0	2	1	0.1325	0.1056
IS	INJECTION SITE	488	B-FIBROMA	1	0	0	0	0	1.0000	0.7926
JE	JEJUNUM	408	M-CARCINOMA	0	0	1	0	1	0.1643	0.1627
KD	KIDNEY	226	B-PAPILLOMA, TRANSITIO	1	0	0	0	0	1.0000	0.8816
KD	KIDNEY	259	M-OSTEOSARCOMA	0	1	0	0	0	0.8852	0.8694
KD	KIDNEY	419	M-LIPOSARCOMA	2	0	0	0	0	1.0000	0.8461
KD	KIDNEY	446	B-ADENOMA, TUBULAR CEL	0	0	1	0	0	0.4663	0.6686
KD	KIDNEY	539	M-CARCINOMA, TUBULAR C	0	0	1	0	0	0.4663	0.6686
LI	LIVER	480	B-ADENOMA, HEPATOCELLU	1	0	0	1	1	0.0725	0.0308
LI	LIVER	493	M-CARCINOMA, HEPATOCEL	2	0	1	0	0	0.8502	0.8361
LU	LUNG	437	M-CARCINOMA, BRONCHIOL	0	0	1	0	0	0.4663	0.6686
LU	LUNG	470	B-ADENOMA, BRONCHIOLAR	0	1	0	0	0	0.7079	0.7639
MA	ADRENAL, MEDULLA	135	B-PHEOCHROMOCYTOMA	10	12	16	25	18	0.0004 (1)	0.0003
MA	ADRENAL, MEDULLA	270	M-MALIGNANT PHEOCHROMO	3	0	0	3	1	0.0793	0.0662
MM	MAMMARY, MALE	265	B-FIBROADENOMA	1	2	3	2	1	0.3350	0.3761

Organ Code	Organ Name	Tumor Code	Tumor Name	CTRO	LOW	MED	MEDHI	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
MM	MAMMARY, MALE	322	M-CARCINOMA	0	1	0	0	4	0.0006 (!)	0.0003
MS	LN, MESENTERIC	535	M-HEMANGIOSARCOMA	0	1	0	0	0	0.7102	0.7651
OC	CAVITY, ORAL	490	M-FIBROSARCOMA	1	0	0	0	0	1.0000	1.0000
PA	PANCREAS	423	M-CARCINOMA, ISLET CEL	1	5	0	1	0	0.8191	0.8395
PA	PANCREAS	487	B-ADENOMA, ACINAR CELL	1	0	0	0	0	1.0000	0.7920
PC	CAVITY, ABDOM	196	M-SCHWANNOMA	0	0	0	0	1	0.0625	0.0007
PC	CAVITY, ABDOM	456	M-HEMANGIOSARCOMA	0	1	0	0	0	1.0000	0.9930
PC	CAVITY, ABDOM	527	M-MALIGNANT PARAGANGLI	0	1	0	0	0	1.0000	0.9930
PI	PITUITARY	14	B-ADENOMA	41	48	41	40	13	0.9890	0.9883
PR	PROSTATE	520	B-ADENOMA	1	0	0	0	0	1.0000	0.7918
SC	SPINAL CORD	435	M-ASTROCYTOMA	0	2	0	0	0	0.7739	0.8122
SK	SKIN	177	B-KERATOACANTHOMA	1	4	3	9	18	0.0000 (!)	0.0000
SK	SKIN	179	M-FIBROSARCOMA	4	4	1	3	4	0.2721	0.2879
SK	SKIN	181	B-FIBROMA	0	4	3	4	2	0.4340	0.4606
SK	SKIN	186	M-SCHWANNOMA	0	1	0	1	2	0.0687	0.0575
SK	SKIN	221	M-CARCINOMA, SQUAMOUS	2	0	0	1	0	0.7459	0.7763
SK	SKIN	277	B-PAPILLOMA, SQUAMOUS	1	1	3	1	4	0.0701	0.0686
SK	SKIN	304	B-ADENOMA, SEBACEOUS G	1	2	0	2	1	0.2641	0.2862
SK	SKIN	326	M-CARCINOMA, BASAL CEL	0	0	0	0	1	0.2286	0.0593
SK	SKIN	442	B-TRICHOEPITHELIOMA	0	0	1	0	0	0.4663	0.6686
SK	SKIN	517	B-LIPOMA	1	0	0	0	0	1.0000	0.7920
SK	SKIN	558	B-ADENOMA, BASAL CELL	0	0	1	2	0	0.2149	0.2195
SM	MUSCLE, SKELETAL	421	M-RHABOMYOSARCOMA	1	0	0	0	0	1.0000	0.7920
SM	MUSCLE, SKELETAL	76	M-FIBROSARCOMA	0	1	0	0	0	0.7833	0.8019
SP	SPLEEN	197	M-SARCOMA, UNDIFFERENT	0	0	0	0	1	0.1629	0.0269
SP	SPLEEN	516	M-HEMANGIOSARCOMA	1	0	0	0	1	0.1306	0.0489
SV	SEMINAL VESICLES	463	M-CARCINOMA	0	0	0	1	1	0.0278	0.0032
TA	CAVITY, THORACIC	569	M-MALIGNANT PARAGANGLI	0	0	0	1	0	0.5000	0.2525
TA	CAVITY, THORACIC	86	M-MESOTHELIOMA	0	1	0	0	0	0.8000	0.8526
TE	TESTIS	198	B-INTERSTITIAL CELL TU	3	2	4	6	2	0.2768	0.2938
TE	TESTIS	482	B-HEMANGIOMA	0	0	0	1	0	0.2373	0.2419
TO	TONGUE	452	B-LIPOMA	0	0	0	1	0	0.4857	0.5090
TO	TONGUE	505	B-PAPILLOMA, SQUAMOUS	0	0	0	1	0	0.2416	0.2433
TY	THYROID	10	B-ADENOMA, C-CELL	18	11	15	6	0	1.0000	0.9998
TY	THYROID	203	M-CARCINOMA, FOLLICULA	0	0	3	0	2	0.1012	0.0954
TY	THYROID	292	B-ADENOMA, FOLLICULAR	2	3	0	1	0	0.8580	0.8624
TY	THYROID	428	M-CARCINOMA, C-CELL	0	3	0	1	0	0.5332	0.6376

UB	URINARY BLADDER	491	M-LEIOMYOSARCOMA	1	0	0	0	0	1.0000	0.8482
UB	URINARY BLADDER	501	B-PAPILLOMA, TRANSITIO	0	0	1	0	0	0.4689	0.6694

Source data: dataset received on 2/24/2005, analysis data R4M21839

*Appears This Way  
On Original*

## Appendix 2: Report on Test for Positive Linear Dose-Tumor Trends in Female Rats

Organ Code	Organ Name	Tumor Code	Tumor Name	CTRO	LOW	MED	MEDHI	HIGH	P-Value (Monte Carlo)	P-Value (Asymptotic Method)
AC	ADRENAL, CORTEX	409	M-CARCINOMA	0	0	3	0	0	0.4767	0.6568
AC	ADRENAL, CORTEX	416	B-ADENOMA	1	2	1	0	1	0.2586	0.2926
AS	AUDITORY SEB GL	251	M-CARCINOMA	0	1	0	0	0	0.4988	0.8649
BR	BRAIN	259	M-OLIGODENDROGLIOMA	0	0	0	1	0	0.3045	0.5701
BR	BRAIN	333	M-MALIGNANT RETICULOSIS	1	0	0	0	0	0.7368	0.8607
BR	BRAIN	415	M-MENINGEAL SARCOMA	1	0	0	0	0	0.7410	0.8559
BR	BRAIN	433	M-ASTROCYTOMA	1	0	0	0	0	0.7424	0.7912
BR	BRAIN	61	M-NEUROBLASTOMA	0	0	1	0	0	0.3895	0.7471
CV	CERVIX	206	M-SARCOMA, STROMAL	0	1	1	1	1	0.8402	0.9045
CV	CERVIX	472	B-LEIOMYOMA	0	0	0	1	0	0.3075	0.1217
HN	HEMATO NEOPLASIA	246	M-MALIGNANT FIBROUS HISTIOCY	0	1	1	0	0	0.6826	0.8528
HN	HEMATO NEOPLASIA	291	M-LEUKEMIA, LARGE GRAN LYMPH	1	0	2	0	0	0.7676	0.8603
HN	HEMATO NEOPLASIA	341	M-SARCOMA, HISTIOCYTIC	0	1	0	0	0	0.4566	0.7621
HN	HEMATO NEOPLASIA	56	M-LYMPHOMA	1	2	0	3	1	0.2261	0.2401
HT	HEART	231	M-ENDOCARDIAL SCHWANNOMA	0	0	0	1	0	0.3045	0.5701
IS	INJECTION SITE	449	B-ADENOMA, BASAL CELL	0	1	0	0	0	0.4545	0.7619
KD	KIDNEY	349	M-LIPOSARCOMA	0	1	0	1	0	0.3108	0.4354
KD	KIDNEY	405	M-CARCINOMA, TUBULAR CELL	0	0	1	0	0	0.2175	0.6631
KD	KIDNEY	463	M-CARCINOMA, TRANSITIONAL CE	0	0	1	0	0	0.2175	0.6631
LI	LIVER	202	B-ADENOMA, HEPATOCELLULAR	0	0	0	2	1	0.1524	0.1254
MA	ADRENAL, MEDULLA	120	B-PHEOCHROMOCYTOMA	1	6	6	8	13	0.0000 !	0.0000
MA	ADRENAL, MEDULLA	466	M-MALIGNANT PHEOCHROMOCYTOMA	0	0	0	1	0	0.2159	0.2282
MF	MAMMARY, FEMALE	29	B-FIBROADENOMA	22	35	29	33	26	0.0978	0.1015
MF	MAMMARY, FEMALE	30	M-CARCINOMA	32	26	29	27	26	0.4675	0.4712
MF	MAMMARY, FEMALE	346	B-MYOEPITHELIOMA	0	0	0	1	0	0.2175	0.2273
OV	OVARY	226	B-SERTOLI CELL TUMOR	0	1	1	1	0	0.6651	0.7989
OV	OVARY	447	M-MALIGNANT GRANULOSA/THECA	0	1	1	0	0	0.4467	0.7473
PA	PANCREAS	384	B-ADENOMA, ISLET CELL	1	1	0	0	0	0.7819	0.8270
PA	PANCREAS	448	M-CARCINOMA, ISLET CELL	0	1	0	0	0	0.4566	0.7621
PA	PANCREAS	473	B-ADENOMA, ACINAR CELL	0	0	0	0	1	0.0625	0.0010
PC	CAVITY, ABDOM	185	M-HEMANGIOSARCOMA	0	0	0	0	1	0.3382	0.1198
PC	CAVITY, ABDOM	461	M-SCHWANNOMA	0	0	1	0	0	0.1986	0.6814

PI	PITUITARY	10	B-ADENOMA	62	63	61	58	43	0.0021	0.0013
PI	PITUITARY	88	M-CARCINOMA	3	2	3	2	1	0.3926	0.4334
Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	MEDHI	HIGH	P-Value (Monte Carlo)	P-Value (Asymptotic Method)
PT	PARATHYROID	412	B-ADENOMA	1	0	0	0	0	0.7479	0.7935
SK	SKIN	128	B-KERATOACANTHOMA	0	1	1	0	1	0.4334	0.5409
SK	SKIN	169	B-FIBROMA	1	2	3	1	1	0.6970	0.7458
SK	SKIN	208	M-FIBROSARCOMA	1	0	1	2	2	0.2711	0.2723
SK	SKIN	214	M-HEMANGIOSARCOMA	0	0	0	0	1	0.3272	0.1065
SK	SKIN	219	M-SCHWANNOMA	0	0	0	1	1	0.2374	0.1973
SK	SKIN	243	B-PAPILLOMA, SQUAMOUS CELL	0	0	0	0	1	0.3068	0.0984
SK	SKIN	263	M-CARCINOMA, SQUAMOUS CELL	0	0	0	0	1	0.3068	0.0984
SK	SKIN	450	M-AMELANOTIC MELANOMA	0	1	0	0	0	0.4566	0.7621
SM	MUSCLE, SKELETAL	112	M-UNDIFFERENTIATED SARCOMA	0	0	0	0	1	0.1769	0.0318
SM	MUSCLE, SKELETAL	330	M-RHABDOMYOSARCOMA	0	1	0	0	0	0.4590	0.7626
SM	MUSCLE, SKELETAL	71	M-FIBROSARCOMA	0	0	1	0	0	0.6247	0.8739
SP	SPLEEN	453	M-SCHWANNOMA	0	0	1	0	0	0.2175	0.6631
SP	SPLEEN	457	M-HEMANGIOSARCOMA	0	0	1	0	0	0.2175	0.6631
ST	STOMACH, GL	323	M-LEIOMYOSARCOMA	0	0	0	0	1	0.1464	0.0190
TH	THYMUS	234	B-THYMOMA	0	2	0	2	1	0.1303	0.1303
TH	THYMUS	41	B-FIBROMA	0	2	0	0	1	0.3190	0.3183
TO	TONGUE	455	B-PAPILLOMA, SQUAMOUS CELL	0	0	1	0	0	0.2175	0.6631
TY	THYROID	126	M-CARCINOMA, FOLLICULAR CELL	0	1	1	2	1	0.1082	0.1040
TY	THYROID	189	M-CARCINOMA, C-CELL	0	1	0	2	0	0.4564	0.4796
TY	THYROID	24	B-ADENOMA, C-CELL	14	13	14	11	7	0.8432	0.8508
TY	THYROID	252	B-ADENOMA, FOLLICULAR CELL	0	1	2	0	1	0.2733	0.3214
UB	URINARY BLADDER	443	B-LEIOMYOMA	0	1	0	0	0	0.4566	0.7621
UT	UTERUS	182	B-POLYP, ENDOMETRIAL, STROMA	5	3	2	4	2	0.3969	0.4192
UT	UTERUS	458	M-CARCINOMA	0	0	2	0	0	0.3931	0.6769
VA	VAGINA	144	B-POLYP, STROMAL	0	2	0	0	0	0.8431	0.8858
VA	VAGINA	380	M-STROMAL SARCOMA	1	0	0	0	0	0.7424	0.7912
VA	VAGINA	479	B-PAPILLOMA, SQUAMOUS CELL	0	0	1	0	0	0.2175	0.6631

Source data: dataset received on 2/24/2005, analysis data R1F218397

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/s/

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Concur with review