

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-884

STATISTICAL REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCES
OFFICE OF BIostatISTICS

Addendum to Statistical Review

NDA: 21,884

Drug Name : Recombinant Human Insulin-Like Growth Factor-I /

Recombinant Human Insulin-Like Growth Factor
Binding Protein-3

rhIGF-I/rhIGFBP-3 (mecasermin rinfabate)

Indication: Treatment of children with
growth failure due to severe growth hormone insensitivity
syndrome (hereditary or acquired) resulting in IGF-I
deficiency and presenting with height standard deviation
score less than or equal to -3 and IGF-I
SDS less than or equal to

Applicant: Inmed Corporation

Dates: Paper and electronic submissions dated 12/31/2004,
05/04/2005, 05/18/2005, 06/01/2005 and 08/15/2005.

Biometrics Division: Division of Biometrics II (HFD-715)

Statistical reviewers: James Gebert, Ph.D.

Concurring Reviewer: J. Sahlroot, Ph. D.

Medical Division: Division of Metabolic and Endocrine Drug Products
(HFD-510)

Clinical reviewer: D. Roman, M.D.

Medical Team Leader: D. Orloff, M.D.

Project manager: E. Galliers

Keywords: Clinical studies, NDA review

The August 15, 2005 submission was received by this reviewer after the statistical review was finalized. This submission was requested by the medical reviewer to facilitate his review. This submission contains no new efficacy data. It does not impact on the conclusions of the statistical review. In the submission the sponsor stated that there was an error in the calculation of a significance level in a table of the sponsor that was included in the statistical review. The P-value of the change from pre-treatment in height velocity at 12 months was <0.0001 not 0.0018. The new table 3 is given below.

Table 3. Height Velocity (cm/yr) in Efficacy Evaluable Population (Cohort #1, n=16)

| | Pre-Treatment | Months 0-6 | Months 0-12 | Change Pre-Tx to Mo 0-6 | Change Pre-Tx to Mo 0-12 |
|---------------------------|---------------|------------|-------------|-------------------------|--------------------------|
| Height Velocity (cm/year) | | | | | |
| Mean | 3.4 | 7.4 | 6.4 | 4.0 | 3.0 |
| SD | 1.9 | 2.0 | 1.6 | 1.8 | 1.3 |
| SE | 0.5 | 0.5 | 0.4 | 0.5 | 0.3 |
| Median | 3.1 | 7.1 | 6.0 | 3.1 | 3.1 |
| Minimum | | | | | |
| Maximum | | | / | | |
| p-value | | | | <0.0001 ¹ | <0.0001 ² |

¹ Wilcoxon signed rank test

² Paired t-test

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James Gebert
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Todd Sahlroot
8/29/2005 02:37:34 PM
BIOMETRICS



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
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1. EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

A significant difference between growth velocity compared to pre-treatment was seen at 6 months for both Cohort #1 and Cohort #2 and at 12 months for Cohort #1 (Cohort #2 has not had 12 months of treatment at the time of cut-off) in Study INSM-110-303.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

Study SK-GHIS-33 is a small PK study that will be discussed because it provides some justification of the dosing regimen.

Study INSM-110-303 is an ongoing study for which 6 month data for Cohort #1 was provided in the sponsor's December 31, 2004 submission and 12 month data for Cohort #1 and 6 month data for Cohort #2 were presented in the sponsor's May 05, 2005 and May 18, 2005 submissions.

A small PK sub-study within Study INSM-110-303 will not be discussed. The purpose of the sub-study, using only 4 subjects, was to compare rhIGF-I/rhIGFBP-3 from two manufacturing sites. It will be left to clinical and biopharm judgment to evaluate whether the product from these two sites are comparable given differences observed.

1.3 STATISTICAL ISSUES AND FINDINGS

With no control group, efficacy in Study INSM-110-303 can only be assessed with respect to pre-treatment growth velocity. A significant difference between growth velocity at 6 months compared to pre-treatment was seen at 6 months for both Cohort #1 and Cohort #2 and at 12 months for Cohort #1 (Cohort #2 has not had 12 months of treatment at the time of cut-off). Efficacy is supported by the fact that Cohort #2 with a higher dose level had a larger growth velocity than Cohort #1. {Since there was no randomization this might also be attributable to difference between the two cohorts.}

The results of the GH provocation test, if given, were not captured in this study. The investigator only answered the question "Peak level of > 29.2 mU/L (>13.3 µg/L) of growth hormone using a GH Provocation test Yes No". The case report forms state that Subjects 7501-105 and 7502-106 had no GH provocation test because they have a diagnosis of growth hormone gene deletion with antibodies. For such patients it is reasonable that no GH Provocation test was done. A GH provocation test was not done on Subject 7801-103. The sponsor stated in their June 1, 2005 submission that this subject was accepted into the trial by the steering committee based on low IGF-I, IGFBP-3, and ALS levels, height SDS, delayed bone growth and a classical phenotype. The case report form for Subject 7601-107 answered no to the question about peak GH level because "GH simulation was normal, but not higher than average", "discussed with Prof. Savage [a member of the study Steering Committee] before study enrollment". The June 1, 2005 submission states that "this subject had a normal growth hormone provocation

test result, based on their (SIC) extreme short stature, and low IGF-I, IGFBP-3, and ALS levels the steering committee accepted him to participate in the trial.”

A significant difference between growth velocity compared to pre-treatment was seen at 6 months (mean change 3.80 cm/year, $P < 0.0001$) and 12 months (mean change 2.84 cm/year, $P < 0.0001$) for Cohort #1 if these 4 subjects are deleted from the analyses. (Subjects 7801-103 and 7601-107 were already not included in the evaluable population for other reasons.)

2. INTRODUCTION

2.1 OVERVIEW

The targeted treatment indication for this product is growth hormone insensitivity syndrome (GHIS). GHIS encompasses a variety of genetic and acquired conditions in which the action of growth hormone (GH) is absent or attenuated. GHIS syndromes have been classified into primary and secondary forms. Primary GHIS, also known as Laron syndrome, is a hereditary defect involving impaired GH receptor function. Affected patients present with dysmorphic features, extreme short stature (height SDS < 3), low serum concentrations of IGF-I, IGFBP-3 and acid labile subunit (ALS) despite high serum GH concentrations. GHIS is an Orphan Indication.

Recombinant human IGF-I (rhIGF-I) has been used to treat GHIS. rhIGF-I by itself has a relatively short half-life (< 15 minutes, according to the sponsor). If given to treat GHIS, it is usually dosed by BID injection because of this extremely short half life. IGF-I commonly binds with insulin-like growth factor binding protein 3 (IGFBP-3) and ALS with the resulting combination having an increased half-life (approximately 15 hours, according to the sponsor). The sponsor states that the half life of IGF-I/IGFBP-3 is several hours.

Giving a rhIGF-I/rhIGFBP-3 combination has the potential of treating patients who have IGF-I deficiency and IGF-I/IGFBP-3 deficiency. With an increased half-life, it can be given by QD injection. Subjects would be able to reduce the number of injections.

IGF-I can activate both the insulin-like growth factor-I receptor (IGF-IR) as well as the insulin receptor (IR) and thus has the potential to induce insulin-like side effects such as hypoglycemia. rhIGF-I/rhIGFBP-3 combined with ALS should stay in circulation and has the potential to avoid insulin-like side effects such as hypoglycemia. There is another potential safety problem that must be evaluated with rhIGF-I/rhIGFBP-3 treatment. Since patients with IGF-I and IGFBP-3 deficiencies may not be producing these chemicals, the body may produce antibodies to these chemicals.

2.1.1 STUDY SK-GHIS-33

This was a small open-label study involving five subjects with a confirmed diagnosis of GHIS of genetic origin. Four of the five subjects were already receiving rhIGF-I therapy

(Pharmacia supplied). On day 1 these four subjects received rhIGF-I by subcutaneous injection twice and blood samples were drawn at pre-determined intervals. After a three month washout they received rhIGF-I/rhIGFBP-3 as a single subcutaneous injection at doses of 0.5 and 1.0 mg/kg with a three day interval between the two doses. Blood samples were drawn at pre-determined intervals after each dose. One of the four subjects received five additionally days of rhIGF-I/rhIGFBP-3 1.0 mg/kg and a single dose of rhIGF-I/rhIGFBP-3 2.0 mg/kg. One rhIGF-I naïve subject received single subcutaneous dose of 1.0 mg/kg and 2.0/mg/kg rhIGF-I/rhIGFBP-3 with a three day interval between the doses. The table below provides the rhIGF-I dose equivalents of the four treatments.

| Treatment | Dose Equivalent of rhIGF-I | | | |
|-----------------------------|----------------------------|-----------|--------------|-------------|
| | µg/kg/dose | µg/kg/day | Nmol/kg/dose | Nmol/kg/day |
| rhIGF-I 80 µg/kg bid | 80 | 160 | 10.5 | 21 |
| rhIGF-I/rhIGFBP-3 0.5 mg/kg | 105.1 | 105.1 | 13.7 | 13.7 |
| rhIGF-I/rhIGFBP-3 1.0 mg/kg | 210.2 | 210.2 | 27.5 | 27.5 |
| rhIGF-I/rhIGFBP-3 2.0 mg/kg | 420.5 | 420.5 | 55.0 | 55 |

The table below provides some PK parameters of the four treatments from this study. The 1.0 mg/kg dose of rhIGF-I/rhIGFBP-3 was closest in C_{max} and AUC₍₀₋₂₄₎ to the daily dose of rhIGF-I 80 µg/kg bid.

| Treatment | T _{max} | C _{max} | AUC ₍₀₋₂₄₎ |
|-----------------------------------|------------------|------------------|-----------------------|
| rhIGF-I 80 µg/kg bid (N=4) | 4.3 hours | 535 ng/mL | 10165 ng hr/mL |
| rhIGF-I/rhIGFBP-3 0.5 mg/kg (N=4) | 19 hours | 458 ng/mL | 8661 ng hr/mL |
| rhIGF-I/rhIGFBP-3 1.0 mg/kg (N=5) | 17 hours | 539 ng/mL | 10095 ng hr/mL |
| rhIGF-I/rhIGFBP-3 2.0 mg/kg (N=2) | 21 hours | 438 ng/mL | 8634 ng hr/mL |

2.1.2 STUDY INSM-110-303

This study is an open-label, prospective, multicenter study to evaluate the safety, tolerability and effectiveness of insulin-like growth factor-I/insulin-like growth factor binding protein 3 (rhIGF-I/rhIGFBP-3) in increasing the height velocity of children and adolescents with growth hormone insensitivity syndrome (GHIS). Subjects will receive a target dose of 1.0-2.0 mg/kg/day rhIGF-I/rhIGFBP-3 once daily by subcutaneous injection for 24 months.

Subjects, to enter the study, had to have a diagnosis of GHIS, such as Laron syndrome. Inclusion criteria included age between 2-18 years; they had to be pre-pubertal; have a height standard deviation score (SDS) ≤ -3 [< -2 before June 30, 2003 protocol amendment]; basal IGF-I SDS ≤ -2; peak stimulated growth hormone (GH) > 13.3 µg/L; and a basal IGFBP-3 SDS ≤ -1. The subjects had to have a documented height velocity assessment from the previous 12 months. Exclusion criteria included bone age > 12 years for girls or > 14 years for boys.

Drug products manufactured at three different facilities were used or will be used in the study:

- Development Drug Product (DDP); development scale clinical drug product manufactured at Insmed former facility in Santa Clara, CA;
- Commercial Drug Product #1 (CDP #1); commercial scale drug product manufactured at Avecia in Billingham, UK;
- Commercial Drug Product #2 (CDP #2); commercial scale drug product manufactured at Insmed Therapeutic Proteins in Boulder, CO.

For Cohort #1, the subjects received 0.5 mg/kg/day of rhIGF-I/rhIGFBP-3 on days 1 and 2 and 1.0 mg/kg/day thereafter. They received medication while hospitalized for the first 4 days. Cohort #1 used DDP for at least the first 12 months.

Cohort #2 initiated chronic therapy with CDP #1. A subset of these patients first participated in a PK sub-study comparing a single dose of DDP and a single dose of CDP #1.

Cohort #3 will initiate therapy with CDP # 2. These patients have not been entered into the study.

Standing height was determined at screening, baseline, month 1, and every 3 months post-baseline. For consistency, standing height measurements were, to the extent possible, taken at each study visit by the same observer, using the same stadiometer at the same time of day. Height velocity was calculated at each post-baseline visit, annualized for that year of treatment, and expressed in cm/year.

Bone age (by x-ray of left hand and wrist) was determined at screening and every 6 months post-baseline. It was analyzed centrally by Professor — using the Tanner-Whitehouse (TW2) RUS maturity score. If, for a single subject, more than one bone age reading was provided for a given date, the results were averaged. [Bone age was also assessed by the FELS Method, not discussed here.]

Height SD scores, or Z-scores, were standardized for age and sex using the UK 1990 standard growth chart. These reference data were provided by the Child Growth Foundation, in the form of LMS tables by age and gender for height; Z scores were calculated using the following equation:

$$Z = \frac{(X/M)^L - 1}{L \cdot S},$$

where X is the measurement, M is the median normative value, L is the power in the Box-Cox transformation, and S is the generalized coefficient of variation. M, L, and S are age and gender dependent.

Serum samples were taken at approximately 18 hours post dose at clinic visits for determination of serum IGF-I, IGF-II, IGFBP-3, and ALS levels.

Standard deviation (SD) scores were calculated for serum IGF-I and IGFBP-3 levels based on age and gender normative data provided by — the supplier of the assays.

To calculate pre-treatment height velocity, heights recorded at least one year prior to entry into the study were obtained. If standing height is not available exactly 365 days prior to the baseline visit, baseline HV was to be calculated in one of the following ways with the denominator adjusted appropriately.

- If a single height measurement is available with a +/- 90-day window, this measurement will be used in the calculation of the baseline HV.
- If multiple height measurements are available in a +/- 90-day window of the date of interest, the measurement taken closest to the date of interest will be used. If there are two height measurements within the +/- 90-day window that are equal close to the date of interest and no other measurement within the window is closer, the two measurements will be used to interpolate the height of interest, and the interpolated value will be used in the calculation of baseline HV.
- If no height measurements are available within the +/-90-day window of the date of interest, the 2 measurements that most closely bracket the date of interest will be used to interpolate the height on the day of interest, and the interpolated value will be used in the calculation of baseline HV.
- If no measurements are available within the +/-90-day window of the date of interest and a pair of measurements to bracket the date of interest is not available, the measurement taken closest to the date of interest will be used in the calculation of baseline HV.

The sponsor defined an evaluable population for data analysis at 6 months, as all subjects who were at least 80% complaint with study dosing while active in the study, were exposed to study drug (at any dose) for a minimum of 159 days from first dose date to last dose date, have efficacy assessments required at study visit 7 (6-Month visit), met selected inclusion/exclusion criteria, and were not major protocol violators. The inclusion /exclusion criteria violations were discussed in the statistical analysis plan.

The sponsor defined an evaluable population for data analysis at 12 months, as all subjects who were at least 80% complaint with study dosing while active in the study, were exposed to study drug (at any dose) for a minimum of 330 days from first dose date to last dose date, have efficacy assessments required at study visit 9 (12-Month visit), met selected inclusion/exclusion criteria, and were not major protocol violators. The inclusion /exclusion criteria violations were discussed in the statistical analysis plan.

The primary efficacy endpoint is the 6-month change in height velocity (HV) from pre-treatment for the evaluable population. Change in height SDS and change in bone age are also evaluated.

The sponsor states that the need for a concurrent control group was obviated by obtaining a documented pre-treatment height velocity in each subject for comparison to on-treatment height velocity. The sponsor stated that it was furthermore unnecessary due to the well-known natural history of the condition, in which the poor height velocity is not expected to improve spontaneously.

From previous rhIGF-I therapy studies, a standard deviation for height velocity was found to be 2 cm/year. Using a two-sided paired t-test and a conservative 2.5 cm/year standard deviation for change in height velocity, 15 subjects are needed to detect a 2 cm/yr change in height velocity from baseline to end of study with 80% power at a 0.05 significance level. The sponsor planned to recruit 60 subjects for this study.

Comparisons from baseline were assessed with a paired t-test (for normally distributed variables) or a Wilcoxon signed rank test.

The protocol states that the primary efficacy and safety analysis will be conducted when approximately 15 subjects have completed 6 months of dosing. The protocol also states that supplementary analyses will be conducted after subjects have completed 12 months of dosing.

2.2 DATA SOURCES

The data for this submission was contained in \\Cdesesub1\n21884\N_000\2004-12-31\crt\datasets and \\Cdesesub1\n21884\N_000\2005-05-04\crt\datasets.

3.0 STATISTICAL EVALUATION.

3.1 EVALUATION OF EFFICACY

3.1.1 STUDY INSM-110-303

Cohort #1 included 19 patients from 11 centers, none of which were in the United States. One center, Professo: — (Turkey) had 5 subjects in the study. All the other investigators had 1 or 2 subjects enrolled in the study. Only 16 of the patients were included in the evaluable population. Two subjects (7601-107 and 7801-103) had protocol violations and were not included. Standing heights could not be obtained reliably from subject 7601-107 because the subject was noncompliant. [This subject had height 75 cm at baseline, 74.5 cm at month 1 and 75 cm at 6 months in the datafile. The analysis of 6 month changes from baseline in height velocity would be significant using 0 for this subject.] This patient withdrew because of a serious adverse event, liver enlargement. This subject later died from respiratory failure. Subject 7801-103 was lost to follow-up. This subject broke contact with the site for over 2 months during which time he went without study medication for an unknown number of weeks. [This subject was showing a change in height velocity of 5.0 cm/year at month 3.] Subject 7401-119 temporarily discontinued treatment for a prolonged period (123 days) and had not completed 6 months of treatment at the time of cutoff for the interim analysis of 6 month data. This patient has not completed 12 months data at the time of submission of 12 month data. This patient would not be evaluable for the 6 month or 12 month analyses because of temporary discontinuation of study treatment for management of ovarian cysts, resulting in < 330 days of treatment with study medication. [This subject was showing above average changes from baseline in height velocity up to month 3.] Two of the subjects, 7301-110 and 8804-114 had their doses decreased to 0.5 mg/kg due to

excessive IGF-I levels at approximately Months 12 and 11 respectively. Subject 8802-112 had approximately 4 weeks of reduced dosing to 0.5 mg/kg following a hypoglycemic episode.

All subjects satisfied the studies inclusion criteria with the exception that some subjects did not have a GH provocation test. The results of the GH provocation test, if given, were not captured in this study. The investigator only answered the question "Peak level of > 29.2 mU/L (>13.3 µg/L) of growth hormone using a GH Provocation test Yes No". The case report forms state that Subjects 7501-105 and 7502-106 had no GH provocation test because they have a diagnosis of growth hormone gene deletion with antibodies. For such patients it is reasonable that no GH Provocation test was done. A GH provocation test was not done on Subject 7801-103. The sponsor stated in their June 1, 2005 submission that this subject was accepted into the trial by the steering committee based on low IGF-I, IGFBP-3, and ALS levels, height SDS, delayed bone growth and a classical phenotype. The case report form for Subject 7601-107 answered no to the GH level question because "GH simulation was normal, but not higher than average", "discussed with Prof. Savage [a member of the study Steering Committee] before study enrollment". The June 1, 2005 submission states that "this subject had a normal growth hormone provocation test result, based on their (SIC) extreme short stature, and low IGF-I, IGFBP-3, and ALS levels the steering committee accepted him to participate in the trial." Subject 8201-101 had a baseline HSD of -2.8 but this subject entered before the June 30, 2003 amendment.

Two of the Cohort #1 subjects (7201-117 and 7202-118) did not have height measurements performed at baseline (start of treatment). Data obtained 3 weeks prior, at a screening visit, were used for baseline height and start date, even though the subjects did not receive therapy for the intervening 3 weeks. Cohort #1 had 13 males and 6 females, a mean age of 8.4 years, a mean height SDS of -6.4, and a mean baseline height velocity of 3.4 cm/year.

Cohort #2 contained 10 subjects from 6 centers. — from Turkey had 4 subjects and —, also from Turkey, had 2 subjects. Only Professor — had subjects in both cohorts, 7 subjects in all. Cohort #2 had 4 males and 6 females, a mean age of 8.6 years, a mean height SDS of -8.0, and a mean baseline height velocity of 2.1 cm/year.

Subject 8301-211 of cohort #2 discontinued drug for approximately one and one-half months due to elevated transaminases at Month 3 and has not completed the 6-month visit and received < 159 days of treatment and is therefore not included in the efficacy evaluable population. [This subject had a change in height velocity at 3 months of — cm/year. The one month change in height velocity was 0, however.] The other 9 subjects have provided 6-month data at the time of the cut-off (April 13, 2005) for the May 4, 2005 submission.

Tables 1 and 2 provide the average serum IGF-I and IGFBP-3 concentration levels for Cohort #1 and Cohort #2, respectively. IGF-I tended to increase over time. IGFBP-3

levels may have reached a plateau after 3 to 6 months. Similar increases were seen in IGF-I SDS and IGFBP-3 SDS scores.

Table 1. Summary of Serum IGF-I and IGFBP-3 Concentrations (nM) for Cohort #1 (Safety Population)¹

| | Baseline | Month 1 | Month 3 | Month 6 | Month 9 | Month 12 |
|---------------------|----------|---------|---------|---------|---------|----------|
| IGF-I (nM) | | | | | | |
| N | 19 | 17 | 18 | 16 | 16 | 13 |
| Mean | 2.2 | 14.4 | 26.1 | 37.1 | 83.9 | 63.0 |
| SD | 1.8 | 9.7 | 19.3 | 40.5 | 108.3 | 105.4 |
| Median | 1.7 | 11.2 | 19.4 | 27.6 | 47.4 | 29.6 |
| Minimum | --- | --- | --- | --- | --- | --- |
| Maximum | --- | --- | --- | --- | --- | --- |
| IGFBP-3 (nM) | | | | | | |
| N | 19 | 17 | 18 | 16 | 16 | 13 |
| Mean | 29.6 | 33.4 | 65.5 | 74.6 | 68.3 | 66.2 |
| SD | 19.2 | 14.3 | 44.8 | 45.2 | 38.1 | 40.6 |
| Median | 26.4 | 32.2 | 55.8 | 66.4 | 49.6 | 46.9 |
| Minimum | --- | --- | --- | --- | --- | --- |
| Maximum | --- | --- | --- | --- | --- | --- |

¹Samples collected just prior to first dose at Baseline and approximately 18 hr after dosing thereafter.

Table 2. Summary of Serum IGF-I and IGFBP-3 Concentrations (nM) for Cohort #2 (Safety Population).

| | Baseline | Month 1 | Month 3 | Month 6 |
|---------------------|----------|---------|---------|---------|
| IGF-I (nM) | | | | |
| N | 10 | 10 | 10 | 9 |
| Mean | 0.7 | 9.0 | 14.8 | 29.9 |
| SD | 1.2 | 3.5 | 7.9 | 13.8 |
| Median | 0.0 | 9.1 | 17.2 | 29.4 |
| Minimum | --- | --- | --- | --- |
| Maximum | --- | --- | --- | --- |
| IGFBP-3 (nM) | | | | |
| n | 10 | 10 | 10 | 9 |
| Mean | 18.4 | 25.2 | 31.3 | 48.4 |
| SD | 10.6 | 4.9 | 10.0 | 16.7 |
| Median | 15.5 | 25.4 | 30.3 | 42.9 |
| Minimum | --- | --- | --- | --- |
| Maximum | --- | --- | --- | --- |

Table 3, below, (Table 7 of the sponsor, Volume 6.2, page 53) provides the results of height velocity at 6 and 12 months for the efficacy evaluable population from Cohort #1. Significant increases from pre-treatment were seen at both 6 and 12 months. All 16 subjects had an increase in height velocity from pre-treatment at both 6 and 12 months.

Table 3. Height Velocity (cm/yr) in Efficacy Evaluable Population (Cohort #1, n=16)

| | Pre-Treatment | Months 0-6 | Months 0-12 | Change Pre-Tx to Mo 0-6 | Change Pre-Tx to Mo 0-12 |
|---------------------------|---------------|------------|-------------|-------------------------|--------------------------|
| Height Velocity (cm/year) | | | | | |
| Mean | 3.4 | 7.4 | 6.4 | 4.0 | 3.0 |
| SD | 1.9 | 2.0 | 1.6 | 1.8 | 1.3 |
| SE | 0.5 | 0.5 | 0.4 | 0.5 | 0.3 |
| Median | 3.1 | 7.1 | 6.0 | 3.1 | 3.1 |
| Minimum | | | | | |
| Maximum | | | | | |
| p-value | | | | <0.0001 ¹ | <0.0018 ² |

¹ Wilcoxon signed rank test

² Paired t-test

Table 4, below, (Table 7 of the sponsor, Volume 6.11, page 50) provides the results of height velocity at 3 and 6 months for the efficacy evaluable population from Cohort #2. Significant increases from pre-treatment were seen at both 3 and 6 months. All 9 subjects had an increase in height velocity from pre-treatment at both 3 and 6 months.

Table 4. Height Velocity (cm/yr) in Efficacy Evaluable Population (Cohort #2, n=9)

| | Pre-Treatment | Months 0-3 | Months 0-6 | Change Pre-Tx to Mo 0-3 | Change Pre-Tx to Mo 0-6 |
|---------------------------|---------------|------------|------------|-------------------------|-------------------------|
| Height Velocity (cm/year) | | | | | |
| Mean | 2.2 | 9.3 | 8.8 | 7.1 | 6.6 |
| SD | 1.5 | 2.7 | 2.0 | 2.8 | 2.6 |
| SE | 0.5 | 0.9 | 0.7 | 0.9 | 0.9 |
| Median | 2.3 | 9.7 | 9.5 | 6.6 | 7.6 |
| Minimum | | | | | |
| Maximum | | | | | |
| p-value | | | | <0.0001 | <0.0001 |

¹ Paired t-test

If we pool the evaluable subjects from Cohorts #1 and #2 for the month 6 changes from pre-treatment we get a mean change of 5.0 cm/year, which is also highly significant. If we compare the mean changes from pre-treatment at month 6 for Cohorts # 1 and #2, We find that Cohort # 2 has a significantly higher change in height velocity (6.1 cm/year vs. 4.3 cm/year) (p=0.0319) even after adjusting for the difference in baseline height velocity. This difference may be because of the higher average dose received by Cohort #2. {Since there was no randomization this might also be attributable to difference between the two cohorts.}

Tables 5 and 6 present the results of the analysis of changes from baseline in height SDS for Cohorts #1 and #2 for the evaluable population.

Table 5. Height SDS in Efficacy Evaluable Population (Cohort #1, n=16)

| | Pre-Treatment | Months 0-6 | Months 0-12 | Change Pre-Tx to Mo 0-6 | Change Pre-Tx to Mo 0-12 |
|------------|---------------|------------|-------------|-------------------------|--------------------------|
| Height SDS | | | | | |
| Mean | -6.4 | -6.1 | -6.0 | 0.33 | 0.49 |
| SD | 2.08 | 2.14 | 2.22 | 0.23 | 0.381 |
| p-value | | | | <0.0001 ² | 0.0017 ¹ |

¹ Wilcoxon signed rank test

² Paired t-test

Table 6. Height SDS in Efficacy Evaluable Population (Cohort #2, n=9)

| | Pre-Treatment | Months 0-6 | Change Pre-Tx to Mo 0-6 |
|------------|---------------|------------|-------------------------|
| Height SDS | | | |
| Mean | -7.9 | -7.5 | 0.4 |
| SD | 1.1 | 1.1 | 0.3 |
| p-value | | | 0.0009 ¹ |

¹ Paired t-test

Bone age is both an efficacy and safety variable. Growth in bone age should be seen if growth is improved but if there is too much growth it could result in early closed epiphyses and reduced final adult height. Tables 7 and 8 presents the results of changes from baseline in bone age (TW2 RUS) for the evaluable population. These analyses support the efficacy of rhIGF-I/rhIGFBP-3.

Table 7. Bone Age (TW2 RUS) in Efficacy Evaluable Population (Cohort #1, n=15)

| | Pre-Treatment | Months 0-6 | Months 0-12 | Change Pre-Tx to Mo 0-6 | Change Pre-Tx to Mo 0-12 |
|--------------------------|---------------|------------|-------------|-------------------------|--------------------------|
| Bone age (years) TW2 RUS | | | | | |
| Mean | 7.0 | 7.4 | 8.7 | 0.3 | 1.5 |
| SD | 3.1 | 3.1 | 2.9 | 0.5 | 0.8 |
| p-value | | | | 0.1991 ¹ | 0.0195 ¹ |

¹ Paired t-test

The largest change in bone age from pre-treatment at 1 year in Cohort #1 was— for subject 7301-110 which is fairly large.

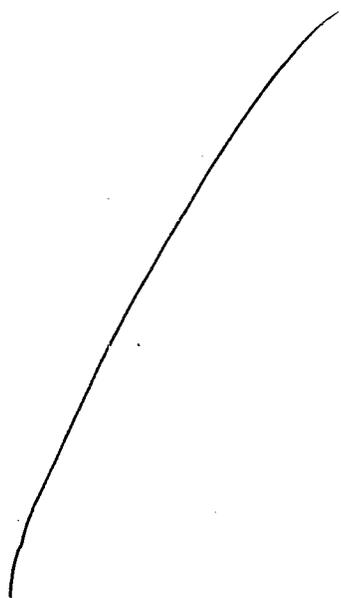
Table 8. Bone Age (TW2 RUS) in Efficacy Evaluable Population (Cohort #2, n=7)

| | Pre-Treatment | Months 0-6 | Change Pre-Tx to Mo 0-6 |
|--------------------------|---------------|------------|-------------------------|
| Bone age (years) TW2 RUS | | | |
| Mean | 5.0 | 6.0 | 1.1 |
| SD | 2.6 | 2.9 | 0.5 |
| p-value | | | 0.0129 ¹ |

¹ Paired t-test

The largest change in bone age from pre-treatment at 6 months in Cohort #2 was 1.7 which is fairly large.

Nine of the 10 subjects of Cohort #2 had baseline negligible ALS values, whereas only 6 of the Cohort #1 subjects had negligible ALS values. The changes in height velocity values at 6 months for these groups with negligible baseline ALS levels were 4.3 cm/year for Cohort #1 and 7.1 cm/year for Cohort #2. [The one subject in Cohort #2, 9401-207, who did not have a negligible ALS level at baseline had only a \approx $\frac{1}{2}$ cm/year change in height velocity at 6 months.] The sponsor shows the following graph of height velocity in the label.



The sponsor states that those with negligible baseline ALS levels may need higher doses.

This graph may be a bit misleading because it focuses on the mean height velocity. If one focuses on changes in height velocity, the situation is not so clear cut. The change in height velocity at 6 months for evaluable subjects in Cohort #1 were 3.8 cm/year for those without negligible baseline ALS levels and 4.3 cm/year for those with negligible baseline ALS levels.

3.2 EVALUATION OF SAFETY

Because of the small number of patients and small amount of drug exposure, it makes the assessment of safety of this drug difficult. There is no control group to do a statistical evaluation of safety. It must be left to clinical judgment to evaluate the safety of rhIGF-I/rhIGFBP-3.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

There are too few subjects to investigate results within subgroups. Since all subjects in the evaluable population increased in growth velocity, there is no indication of lack of efficacy in some subgroup.

5.0 SUMMARY AND CONCLUSIONS

A significant difference between growth velocity compared to pre-treatment was seen at 6 months for both Cohort #1 and Cohort #2 and at 12 months for Cohort #1 (Cohort #2 has not had 12 months of treatment at the time of cut-off) in Study INSM-110-303.

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