



# Long-term Therapy with rhIGF-1: No Evidence of Neutralizing Antibodies

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## BACKGROUND

Recombinant human insulin-like growth factor-1 (rhIGF-1 or mecasermin) is a 70 amino acid protein currently being reviewed by the FDA as a long-term replacement therapy for children with growth failure caused by primary IGF-1 deficiency (Primary IGFD).

Subcutaneous injections of protein therapeutics, such as rhIGF-1, can induce antibodies in recipients. Therefore in the pre-clinical and clinical rhIGF-1 drug development program, anti-IGF-1 antibodies were measured routinely using an ELISA developed specifically for this purpose.

## AIMS

- 1) To evaluate the antigenicity of life-time treatment with rhIGF-1 in the rat.
- 2) To investigate the presence and effect of antibodies to IGF-1 in children with Primary IGFD treated long term with rhIGF-1.

## ANIMAL STUDY

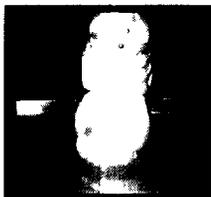
### METHODS

- Male and female Sprague Dawley rats (75/group) were given daily sc injections of placebo (0.25, 1, 4 or 10 mg/kg/day rhIGF-1) rotated between 4 sites on the dorsal skin for 2 years.
- Rats were housed individually, food and water were provided *ad libitum* and food intake and body weights were measured regularly.
- Sake-like animals (15/group) were bled intermittently to measure glucose, rhIGF-1, and anti-IGF-1 antibodies.
- Sera were tested for anti-IGF-1 antibodies using an assay developed by Genentech.
- The study, a formal toxicology study under GLP conditions was conducted at Covance Laboratories.

### RESULTS

Life-time treatment with rhIGF-1 induced dramatic increases in body growth with some rats weighing up to 1.5 kg (Figure 1) with the weight gain being maintained. There were no detectable anti-IGF-1 antibodies in this study.

Figure 1. Lifetime Therapy With rhIGF-1 Produces Giant Rats



## HUMAN STUDY

### METHODS

- 22 children with short stature due to Primary IGFD were studied.
- Treatment with rhIGF-1 at doses primarily between 0.080 to 0.120 mg/kg BID for 2 years.
- A formal antibody assessment by blood sampling over the 2 years.
- Sera were tested for the presence of antibodies to rhIGF-1 by ELISA.

### RESULTS

- During the first year of treatment with rhIGF-1, 11 of the 22 subjects had a positive titer for anti-IGF-1 antibodies at one or more times.
- Antibodies were generally of low titer and, when present at the start of the study, did not increase in titer during the 2 year study.
- To assess the significance of the antibodies, the growth of the children with and without antibodies was compared. During the first year of treatment, the mean  $\pm$  SD for height velocity in the 11 subjects without antibodies was  $7.3 \pm 3.1$  cm/yr compared to  $7.9 \pm 2.1$  cm/yr in subjects with antibodies (Table 1).
- The difference was not statistically significant (two tailed p value = 0.54).
- Therefore, in these children, antibodies did not seem to significantly compromise efficacy by affecting the growth response to rhIGF-1.

Table 1. Subjects With and Without Antibodies to IGF-1

	Subjects Without Antibodies (n=11)	Subjects With Antibodies (n=11)
Females/Males (n)	2/9	4/7
	Mean $\pm$ SD (range)	Mean $\pm$ SD (range)
Baseline Age (years)	7.4 $\pm$ 4.6 (1.7 to 15.2)	6.3 $\pm$ 3.8 (2.3 to 13.5)
First Year Height Velocity (cm/yr)	7.3 $\pm$ 3.1 (2.3 to 12.4)	7.9 $\pm$ 2.1 (5.3 to 11.3)

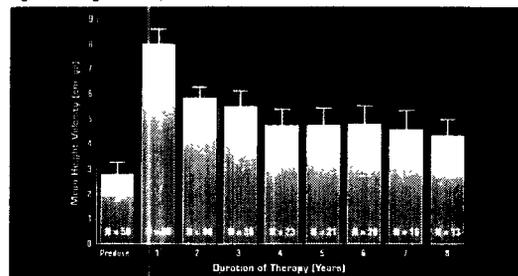
## ACKNOWLEDGEMENTS

Louis Underwood, Steven Chernausk, Noel Dybdal, Michael Ewell, Brian Christian, Paul Fielder, Derek Kennedy, George Shoop, Art Thakur, Janet Clarke, Jane Bailly

## RESULTS (CONT)

The growth response to long term therapy with rhIGF-1 in an expanded cohort of short children with Primary IGFD is shown below. These data also indicate that long term rhIGF-1 therapy causes a prolonged and sustained growth response which would not occur if significant neutralizing anti-IGF-1 antibodies were present.

Figure 2. Height Velocity on rhIGF-1



95% Confidence Interval

There were no apparent immunotoxic safety effects detected in the subjects positive for antibodies. In addition, despite up to 11.5 years exposure to rhIGF-1 in the 71 pediatric subjects with Primary IGFD, no safety effects related to immunotoxicity have been detected.

## CONCLUSIONS

- After only several days of dosing with rhGH in rats, powerful neutralizing anti-rhGH antibodies can be generated that inhibit growth (Fielder et al, *Endocrinol.* 137: 1913-20, 1996). In contrast, there were no anti-IGF-1 antibodies detected during life-time treatment with rhIGF-1, and giant rats resulted, suggesting that rhIGF-1 does not induce neutralizing antibodies. Compared to rhGH which is very immunogenic, rhIGF-1 is non-immunogenic in the rat.
- The present animal and human data show that subcutaneous injections of rhIGF-1 do not induce significant antibody responses. Therefore, the long-term efficacy of rhIGF-1 in children with short stature will likely not be compromised by the generation of neutralizing anti-IGF-1 antibodies.