



# Efficacy of long-term treatment with recombinant human IGF-1 in children with GH insensitivity

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## INTRODUCTION

Several reports have shown that statural growth is improved by replacement therapy with recombinant human (rh)IGF-1 in children with IGF-1 deficiency resulting from insensitivity to growth hormone (GH). Most of these reports, however, contained results on small numbers of children and/or treatment for brief intervals. We now report rhIGF-1 treatment results for 54 children in a 65 subject cohort who have completed at least one year of rhIGF-1 therapy. The data represent a total of 231 treatment-years.

## METHODS

The key inclusion criteria for this multi-center open label study were

- Age  $\geq 2$  years
- Open epiphyses
- Height SDS  $< -2$
- Height velocity  $< 50$ th percentile
- Serum IGF-1 SDS  $< -2$

Initially, dose selection was derived by titration to tolerance (avoidance of hypoglycemia). Thereafter, individualization of dosing continued to occur based on safety and efficacy considerations. rhIGF-1 from Genentech, Inc. was used throughout. Bone age was assessed by serial X-ray of the left hand and wrist.

## RESULTS

The mean duration of rhIGF-1 treatment was 3.6 years (range, 0.5-10.5 years), beginning treatment at an age of  $6.5 \pm 3.7$  years ( $\pm$ SD). The subjects consist of 36 males and 18 females, 45 with phenotypic Laron syndrome, 7 with growth-attenuating antibodies to GH following GH therapy, and 2 with unspecified defects producing GH insensitivity. All patients were severely deficient in IGF-1, with a median baseline serum IGF-1 concentration of 20 ng/ml. At the start of therapy, mean height was  $88.7 \pm 18$  cm, corresponding to a mean height age (HA) of  $2.5 \pm 1.9$  y and HT-SDS of  $-6.7 \pm 1.7$ .



**Figure 1. Height Velocity on rhIGF-1 (Mean, 95% CI)**

Twice daily subcutaneous injections of rhIGF-1 at doses of 80-120  $\mu$ g/kg resulted in an improvement in height velocity (HV) from  $2.6 \pm 1.6$  cm/y before treatment, to  $8.0 \pm 2.3$  cm/y at 1 year ( $P < 0.0001$ , paired t-test). Pre-treatment HV data were available for 48 of the 54 children.



**Figure 2. Cumulative Change in HT-SDS on rhIGF-1, by Year of Therapy (Mean, 95% CI)**

The pretreatment HT-SDS was  $-6.5 \pm 1.7$ . By the end of the first year, the mean HT-SDS increased by 0.79 ( $p < 0.0001$ , paired t-test) and had increased by 1.44 at year 8.



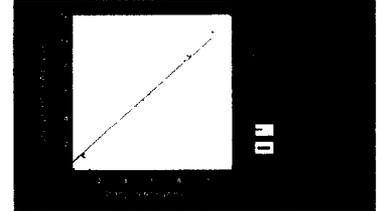
**Figure 3. First Year Dose Response for Height Velocity**

The average daily dose of rhIGF-1 is shown plotted against the individual height velocity for the first year of treatment. The slope of this dose-response relationship was positive and significant ( $r = 0.0004$ ,  $N=54$ ).

## Change in Bone Age

All subjects with a baseline bone age evaluation and a second bone age evaluation after at least one year of treatment were included in the analysis ( $N=34$ ). The mean change in chronological age was  $4.9 \pm 3.3$  years and the mean change in bone age was  $5.2 \pm 3.2$  years. The difference between the change in chronological age and bone age was not significant ( $p = 0.2$ ).

**Figure 4. Change in Bone Age vs Change in Chronological Age**



## CONCLUSIONS

- rhIGF-1 therapy produces prompt and significant increases in HV and HT-SDS during the first year of treatment
- Increments in HV and HT-SDS persist for up to eight years of treatment
- There is a dose-response relationship between average daily dose of rhIGF-1 and HV during the first year
- rhIGF-1 doses between 80 and 120  $\mu$ g/kg BID SC appear most effective in promoting statural growth
- At these doses, children had no undue advancement in bone age

## SUMMARY

Prolonged rhIGF-1 treatment of IGF-1 deficiency in children with GH insensitivity produces significant and persistent improvement in the growth rate and improvement in the relative progression of skeletal and height maturation.

See poster P3-450 for safety data from this study.

**Acknowledgements:** The authors wish to thank Genentech, Inc. for their support of these studies. The Growth Hormone Insensitivity Syndrome (GHIS) Collaborative Study Group consists of Drs. M. C. Amiaz, S. Blithen, M. Cappa, W. Cleveland, D. Donaldson, V. Duncan, R. Ehrlich, L. Ghizzoni, J. Heinrich, M. Miras, A. Rosenblom, N. Sehen, V. Sockolovskaya, D. Transue, and A. Woloska.