IGF-1 Values in Hypochondroplasia and Effects of Vosoritide

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BACKGROUND

- Hypochondroplasia (HCH) is a form of disproportionate short stature caused by activating variants in *FGFR3*.
- Vosoritide is a C-type natriuretic peptide (CNP) analog that promotes growth by inhibiting the MAPK pathway downstream from FGFR3 on the chondrocytes.
- We previously reported the results of a Phase II study in children with HCH showing an increase in height velocity (HV) of 1.81 cm/year and gain of 0.36 in height SD over 12 months.
- The GH/IGF-1 axis has not been well studied in children with HCH.
- The objective of this study was to describe IGF-1 levels in children with HCH and explore whether there is an interaction between vosoritide therapy and IGF-1.

METHODS

- We conducted a Phase II trial of daily vosoritide 15mcg/kg/day
- 24 prepubertal subjects with HCH (12 F, mean age 5.9+/-2.3 years, mean height -3.29+0.68 SD) for 12 months, after a 6-month observation period.
- Anthropometrics and IGF-1 (LC/MS) were measured every 6 months and trended over time.
- Pearson correlations were performed between IGF-1 Z-score and height Z-score at baseline.
- One sample t-test was used to compare IGF-1 Z scores to the reference (0). Paired t-test was used for the mean difference between different stand points.

RESULTS

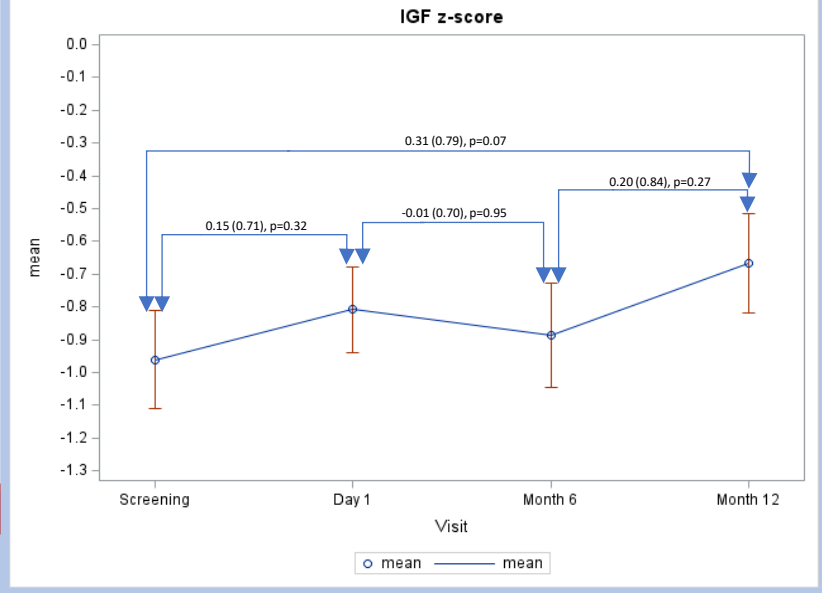

Fig. 1: Change of IGF-1 Z score over time, at a 6 months interval. Points represent mean values, error bars represent +/- 1 standard deviation (SD) from the mean. Comparative analysis of mean IGF-1 Z-scores at different times also shown here. Arrows indicating timepoints of comparison, mean (SD) and p-value shown on top.

	Change in AHV (Day 1 to Month 12)	Change in Height SD (Day 1 to Month 12)
IGF-1 Z-score at Day 1	0.12 (0.59)	0.21 (0.34)
IGF-1 Z-score at Month 12	-0.04 (0.84)	-0.08 (0.70)

Table 1: Pearson correlation between IGF-1 Z score with change in height velocity and change in height SD. Values represent coefficient, p-value in parenthesis. AHV= annualized height velocity, SD= standard deviation

RESULTS

- IGF-1 in patients with HCH is below average compared to general population at all time points (p<0.0002)
- There is no significant change in IGF-1 over the course of treatment with vosoritide.
- Change in IGF-1 between observation and treatment period was not significantly different (mean Delta= 0.01, SD 1.22, p=0.97)
- IGF-1 at baseline did not correlate with height at baseline.
- IGF-1 at Day 1 or Month 12 did not correlate with growth outcomes in the study.

CONCLUSIONS

- ✓ *Patients with HCH have lower IGF-1 values than the average population, indicating a possible interaction between the FGFR3 and GH/IGF-1 axis.*
- ✓ *There is no evidence of an effect on IGF-1 with vosoritide treatment.*
- ✓ *Vosoritide treatment increased height velocity independently of a change in IGF-1.*
- ✓ *Data from a larger patient population are needed to confirm these findings.*

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