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Sustained Suppression of IGF1 with AZP-3813, a Bicyclic 16-Amino Acid Peptide Antagonist of the Human Growth Hormone Receptor and a Potential New Treatment for Acromegaly

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INTRODUCTION: Acromegaly is typically caused by an adenoma of the somatotroph cells of the pituitary that hyper-secretes growth hormone (GH), which in turn stimulates excess insulin-like growth factor 1 (IGF1) production and the resulting overgrowth of tissues and disease manifestations. Suppression and control of IGF1 levels in acromegaly through medical therapy is based on either suppressing GH secretion from the pituitary or inhibiting GH action by preventing interaction with its receptor. AZP-3813 is a 16-amino acid, bicyclic peptide antagonist of the GH receptor (GHR) that was derived from peptide sequences discovered using a unique, cell-free in vitro transcription-translation system screened against the human GHR, and that was optimized by rational design to increase binding affinity, solubility and half-life. In previous studies, AZP-3813 was demonstrated to suppress IGF1 secretion in juvenile rats in a dose-related manner. To examine the ability of chronic AZP-3813 treatment to maintain suppression of IGF1 levels, we injected normal, 5-week old (~150g), male Sprague Dawley rats subcutaneously either with vehicle or with AZP-3813 at doses of either 10 or 30mg/kg QD for 19 days (n=7/group).

AZP-3813: 16 Amino Acid, Bi-Cyclic Peptide

- MW = 2479.9
- hGH-R affinity (K_D) = 2.9nM
- hGH-R antagonism (IC_{50}) = 9.9nM
- 2H Human Plasma Stability = 88.5%
- rGH-R affinity (K_D) = 18.5nM
- 2H Rat Plasma Stability = 105.9%

Rat Pharmacokinetics (3mg/kg, sc, 750g rat)

- $T^1/_2$ = 11.2 hours
- T_{max} = 3.3 hours
- C_{max} = 8547ng/ml

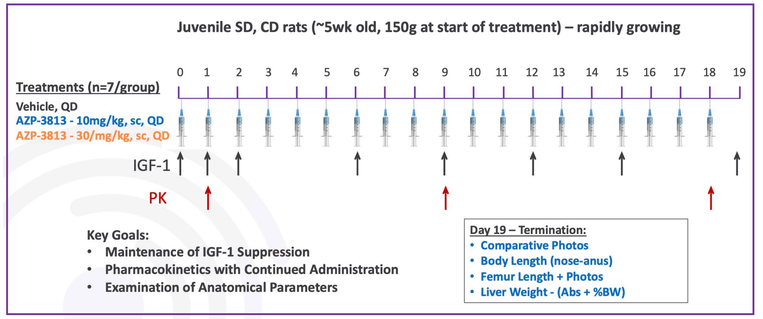


FIGURE 1. Study Design – Effect of chronic QD administration of AZP-3813 on IGF1 and related parameters in juvenile rats

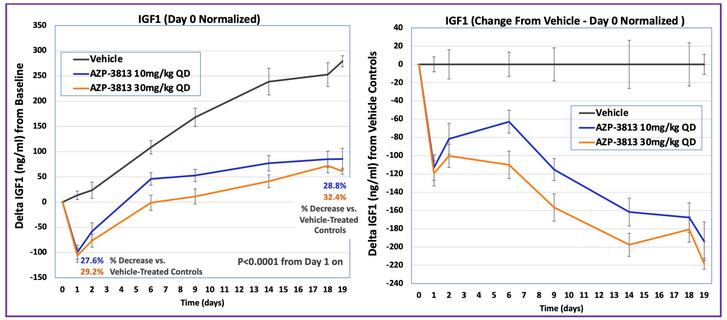
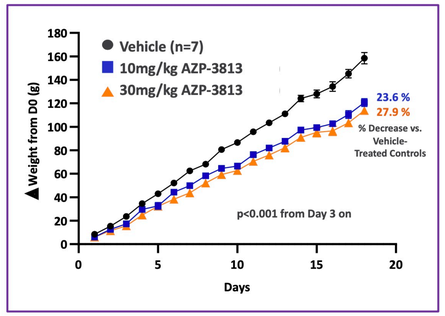


FIGURE 2. AZP-3813 produced a rapid decrease in IGF1 within 24 hours, that, with continued QD treatment, maintained a similar magnitude of IGF1 suppression through the end of the study, despite increasing IGF1 levels in the vehicle-treated controls



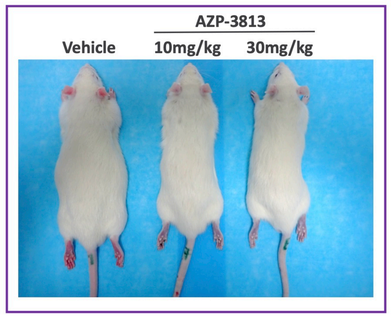


FIGURE 3 and 4. Over the course treatment, body weight of vehicle-treated rats increased by ~2-fold. AZP-3813 suppression of IGF1 resulted in significantly decreased body weight gain, as well as decreased body length

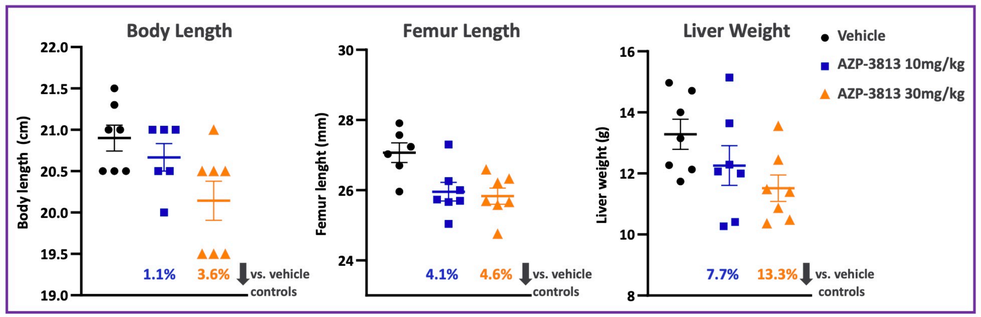


FIGURE 5. AZP-3813 suppression of IGF1 resulted in significantly decreased IGF1-influenced anatomical parameters

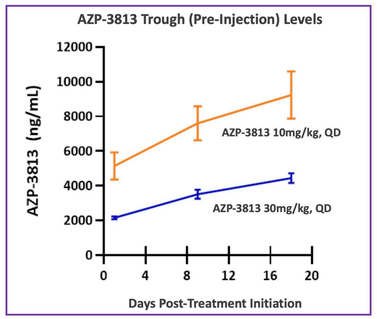


FIGURE 6. Increasing blood levels of AZP-3813 with repeated injection, indicating compound accumulation. Desirable for ensuring continued ability to out-compete endogenous GH from reaching its receptor

Summary of Effects of AZP-3813 on IGF1 and Associated Parameters in Juvenile Male Rats:

- Maximal suppression of IGF1 attained within 24 hours of initial dosing
- The magnitude of IGF1 suppression was maintained through the end of the study with continued, daily treatment, despite rising IGF1 levels observed in the vehicle-treated control rats
- Clear suppression of IGF1-influenced parameters with repeated, daily AZP-3813 administration, i.e. growth rate, body length, and anatomical parameters
- Blood levels of AZP-3813 increased with repeated, daily administration, indicating compound accumulation

CONCLUSION:

These results demonstrate that with continued treatment, the potent GHR antagonist activity exhibited by AZP-3813 translates to highly effective, sustained in vivo suppression of IGF1 levels and associated parameters, and support its development as a potential therapy for acromegaly.

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