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AZP-3813, a Bicyclic, 16-Amino Acid Peptide Antagonist of the Human Growth Hormone Receptor, Effectively Suppresses IGF1 in Beagle Dogs

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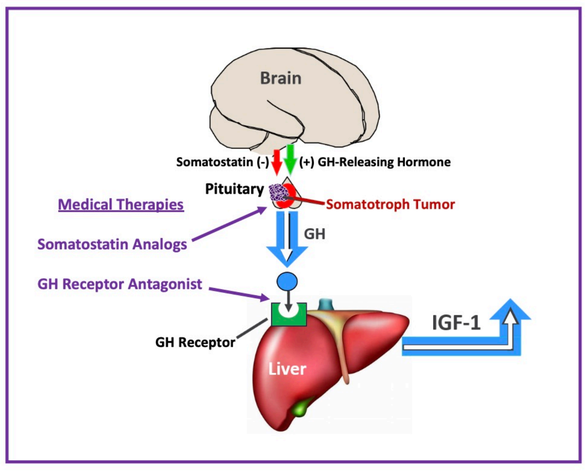
INTRODUCTION: Acromegaly is typically caused by an adenoma of the somatotroph cells of the pituitary that hyper-secretes GH, which in turn stimulates excess insulin-like growth factor 1 (IGF1) production and the resulting overgrowth of tissues and disease manifestations. Suppression and control of IGF1 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 (Figure 1). 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. Previously, AZP-3813 was demonstrated to suppress IGF1 secretion in juvenile rats in a dose-related manner, and to maintain IGF1 suppression for extended periods when given daily. In this study, we examine the ability of AZP-3813 treatment to suppress IGF1 levels in normal dogs

FIG 1. Basis of medical therapy to control excess IGF1 in acromegaly



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
- rGH-R affinity (K_D) = 18.5nM

Rat Pharmacokinetics

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

FIG 2: Dose-related suppression of IGF1 in juvenile rats with single injection of AZP-3813 (data normalized to pre-dose levels; means ± SEM)

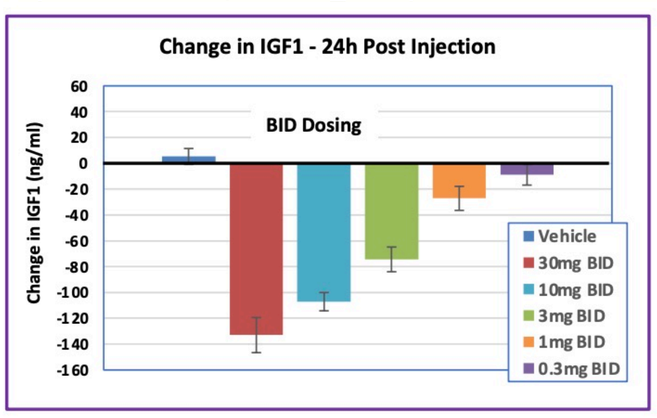


FIG 3: Suppression of IGF1 in juvenile rats maintained with repeated, daily AZP-3813 injection versus pegvisomant (means ± SEM)

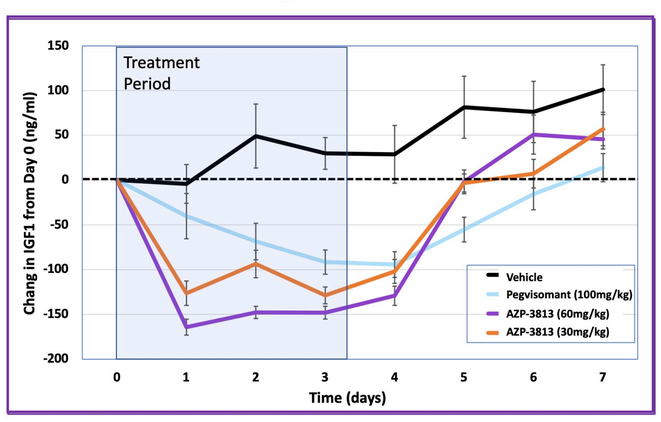


FIG 4: AZP-3813 treatment suppresses IGF1 as well as between and within individual animal IGF1 variability in juvenile rats

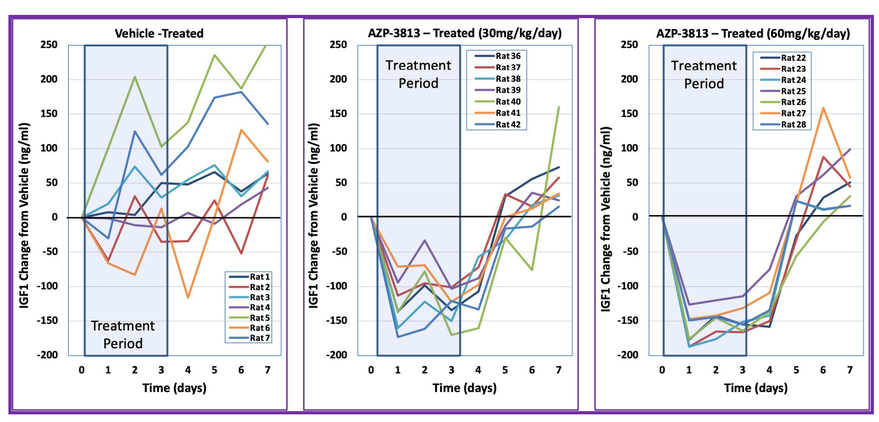


FIG 5: Study design part 1 – Single injection of 0.1 and 10mg/kg AZP-3813 in male Beagle dogs (n=3, mean weight = 9.7 ± 1.1kg)

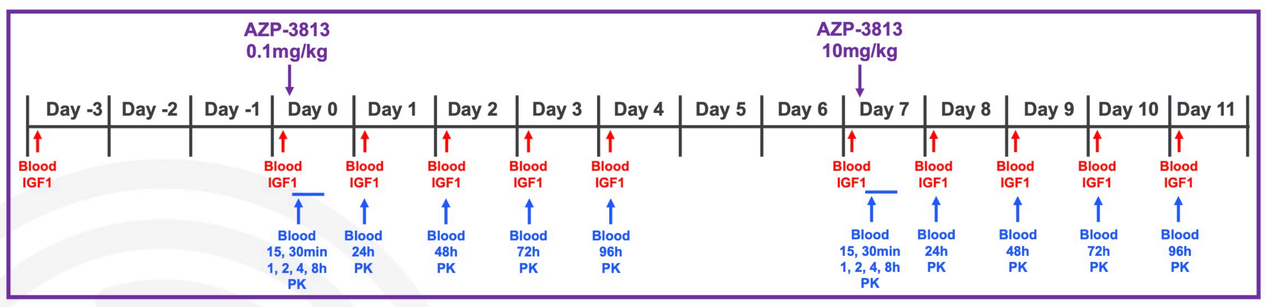


FIG 6: Study design part 2 – Repeat injection of 1.0mg/kg AZP-3813 in male Beagle dogs (n=3, mean weight = 9.9 ± 0.9kg)

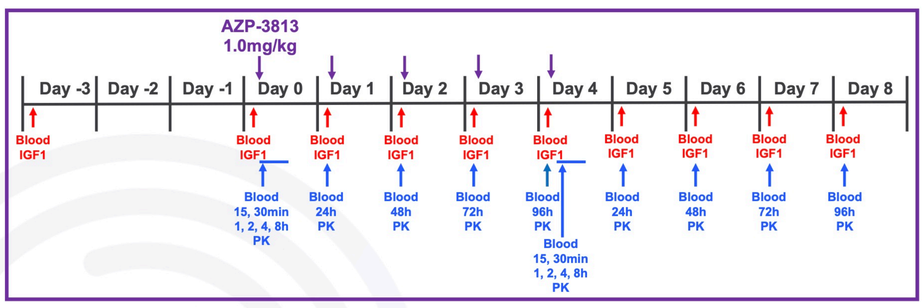


FIG 7: Dose-related suppression of IGF1 24h after single AZP-3813 injection in Beagle dogs (means ± SEM)

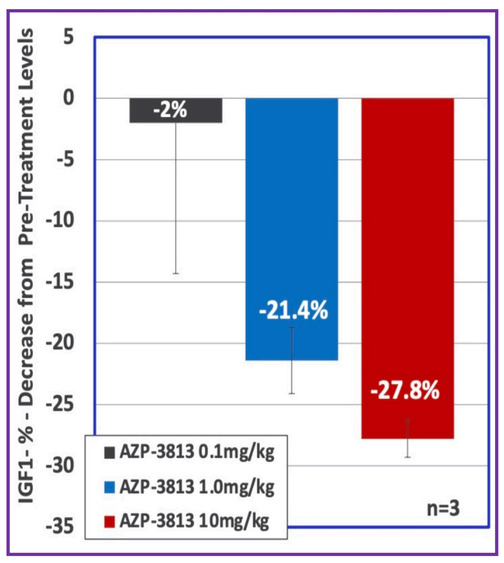


FIG 8: A) Repeated injection of 1mg/kg AZP-3813 maintains IGF1 suppression, and B) Sustained suppression of IGF1 with single injection of 10mg/kg (means ± SEM)

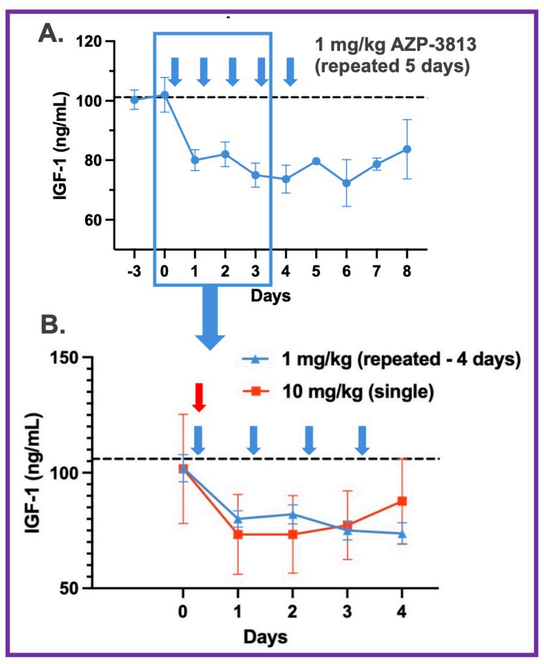


FIG 9: Dose-related blood levels of AZP-3813 following single injection. Note different scales (means ± SEM)

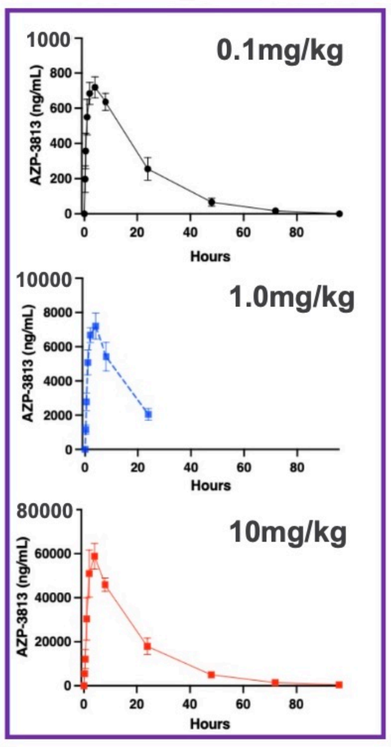


FIG 10: Parallel dose-related elimination of AZP-3813 following single injections (mean ± SEM)

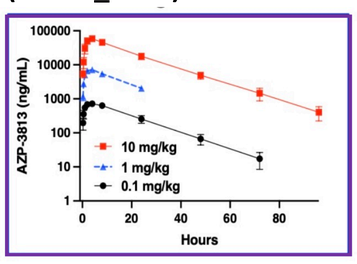


FIG 11: Half-life of AZP-3813 in Beagle dogs.
Mean = 14.2 ± 0.47 hours

Dose	Half-Life (h)
0.1mg/kg	15.1
1.0mg/kg	13.2
10mg/kg	14.3

FIG 12: Increased Cmax after 5-days repeated injection of 1.0mg/kg AZP-3813 demonstrates compound accumulation (means ± SEM)

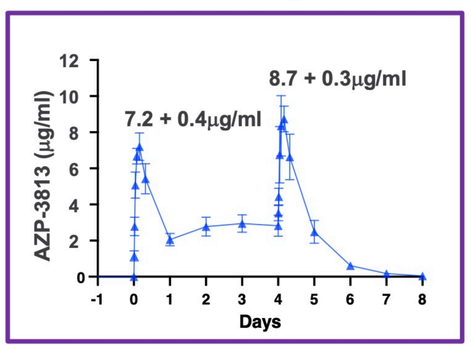
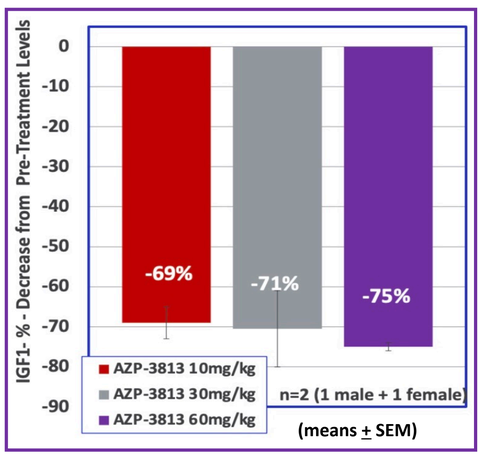


FIG 13: Daily injection of 10mg/kg and higher doses of AZP-3813 for 7 days resulted in significantly greater IGF1 suppression in Beagle dogs



SUMMARY FIGURES 7 - 13:

- Single injection of AZP-3813 induced a rapid, dose-related suppression of IGF1 in normal Beagle dogs within 24 hours
- Repeated injection of 1mg/kg AZP-3813 maintained an average 26% IGF1 suppression through 72 hours following the fifth injection, while single injection of 10mg/kg AZP-3813 induced and sustained a similar degree of IGF1 suppression through 72 hours post-injection
- Single injection of AZP-3813 in Beagle dogs induced dose-proportional AZP-3813 blood levels with Cmax attained at 4 hours post-injection,
- parallel elimination curves, and mean ± SEM half-life of 14.2 ± 0.47 hours
- With 5 days repeated administration of 1mg/kg AZP-3813, the Cmax of blood AZP-3813 increased by ~20%, indicating compound accumulation
- In a subsequent study (Fig. 13), daily injection of 10mg/kg and higher doses of AZP-3813 resulted in significantly greater IGF1 suppression in Beagle dogs

CONCLUSION:

The results of the current study demonstrate that the potent GH receptor antagonist activity exhibited by AZP-3813 translates to effective, sustained in vivo suppression of IGF1 levels in normal Beagle dogs, and further support the development of AZP-3813 as a potential therapy for acromegaly