AZP-3813, a Bicyclic 16-Amino Acid Peptide Antagonist of the Human Growth Hormone Receptor as a Potential New Treatment for Acromegaly

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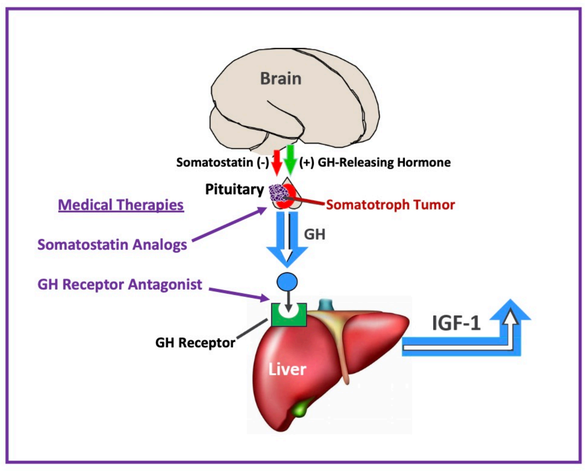
INTRODUCTION: Acromegaly is typically caused by an adenoma of the somatotroph cells of the pituitary that hyper-secretes growth hormone (GH), which in turn stimulates excess insulin-like growth factor 1 (IGF1) production and the resulting overgrowth of tissues and disease manifestations. Suppression 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 (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. To determine if the potent GH receptor antagonism displayed in vitro translates to in vivo efficacy, the ability of AZP-3813 to suppress IGF1 levels in normal juvenile rats was examined.

FIGURE 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
- 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 2: Study Design -AZP-3813 Dose-Related Suppression of IGF1

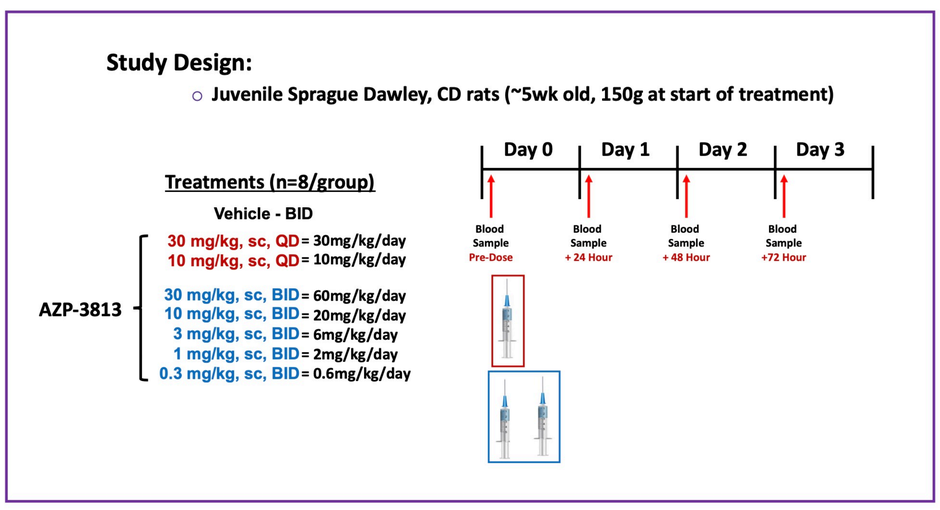


FIGURE 3: AZP-3813 Dose-Related Suppression of IGF1 With BID Dosing (data normalized to pre-dose)

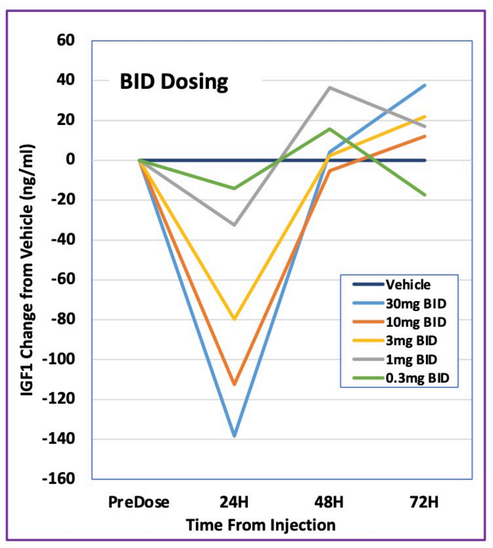
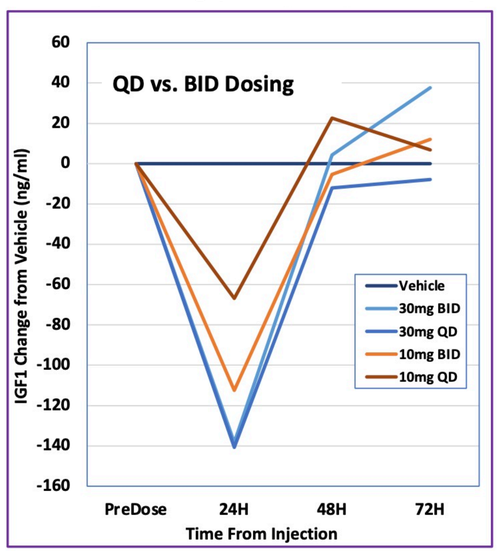


FIGURE 5: AZP-3813 Dose-Related Suppression of IGF1 With QD vs. BID Dosing (data normalized to pre-dose)



SUMMARY FIGURES 2-6:

- AZP-3813 induced a rapid, dose-related suppression of IGF1 in normal, juvenile rats
- Maximal effect was observed 24 hours after injection, with IGF1 returning to vehicle levels by 48 hours and showing a "rebound elevation" at 72 hours
- Similar efficacy was observed with 30mg/kg administered either QD or BID, indicating full efficacy with QD dosing and the attainment of maximal effect

FIGURE 4: Suppression of IGF1 24H after AZP-3813 BID Dosing

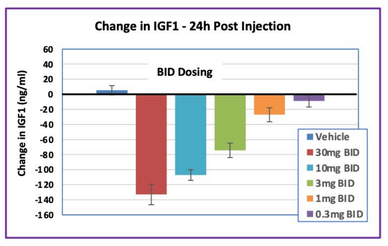


FIGURE 6: Suppression of IGF1 24H after AZP-3813 QD or BID Dosing

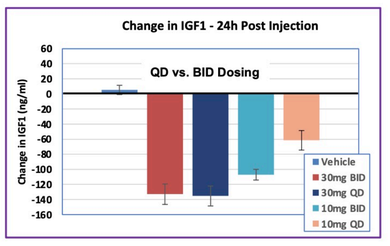


FIGURE 7: Study Design - AZP-3813 Repeated Dose Suppression of IGF1

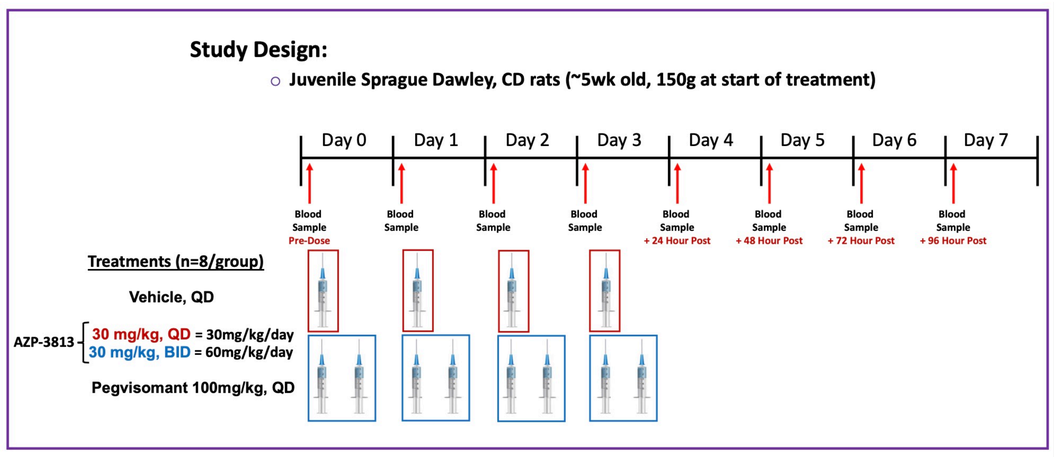


FIGURE 8: Repeated Dose Suppression of IGF1 with AZP-3813 and Pegvisomant

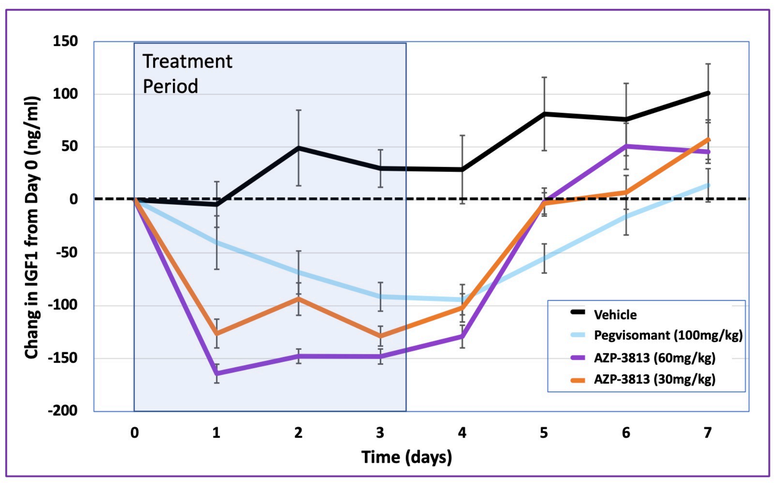
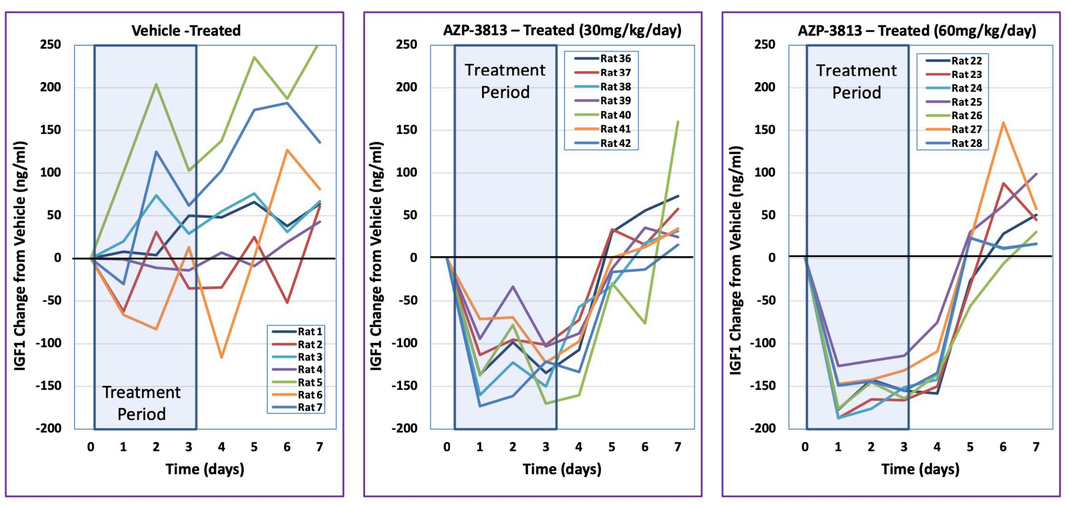


FIGURE 9: AZP-3813 Treatment Suppresses IGF1 as well as between and within individual animal IGF1 variability



SUMMARY FIGURES 7-9:

- AZP-3813, administered at 30mg/kg, either QD or BID, induced a rapid suppression of IGF1 in normal, juvenile rats within 24 hours
- With continued AZP-3813 treatment, the suppression of IGF1 was maintained through 24 hours after the last injection
- The commercially available GH antagonist, pegvisomant, administered at 100mg/kg QD, induced a gradual suppression of IGF1 that reached a similar magnitude of suppression as observed with AZP-3813 only after 4 days of treatment
- IGF1 levels gradually returned to pre-dosing levels by 48 hours after the last injection
- Examining patterns of IGF1 in individual, vehicle-treated rats, significant variability was observed both between animals and within the same animal. Treatment with AZP-3813 not only suppressed IGF1, but greatly reduced and controlled the variability.

CONCLUSION: The results of the current studies demonstrate that the potent GH receptor antagonist activity exhibited by AZP-3813 translates to effective in vivo suppression of IGF1 levels, and support its development as a potential therapy for acromegaly.