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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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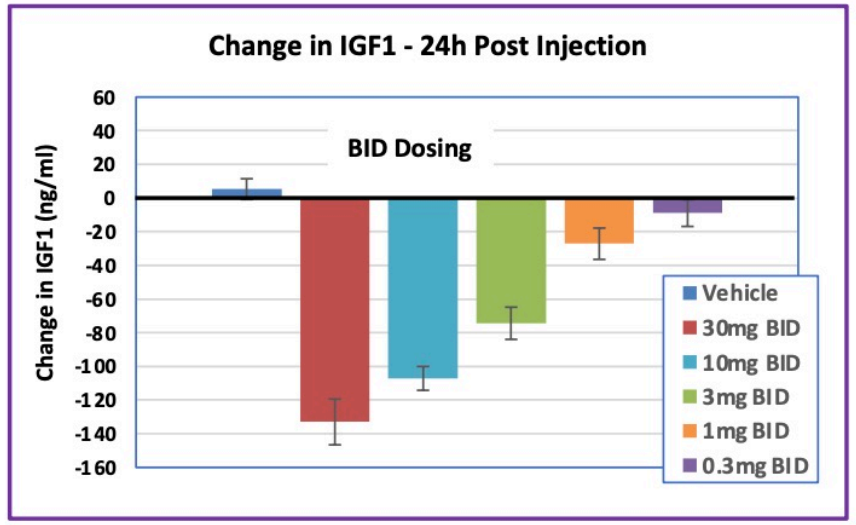
AZP-3813: 16 Amino Acid, Bi-Cyclic Peptide Antagonist of hGH Receptor

- 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%



Rapid, Dose-Related Suppression of IGF1 In Juvenile Rats

Present study examines the ability of chronic, daily administration of AZP-3813 treatment to maintain suppression of IGF1 levels and to suppress IGF1-related parameters in the juvenile rat

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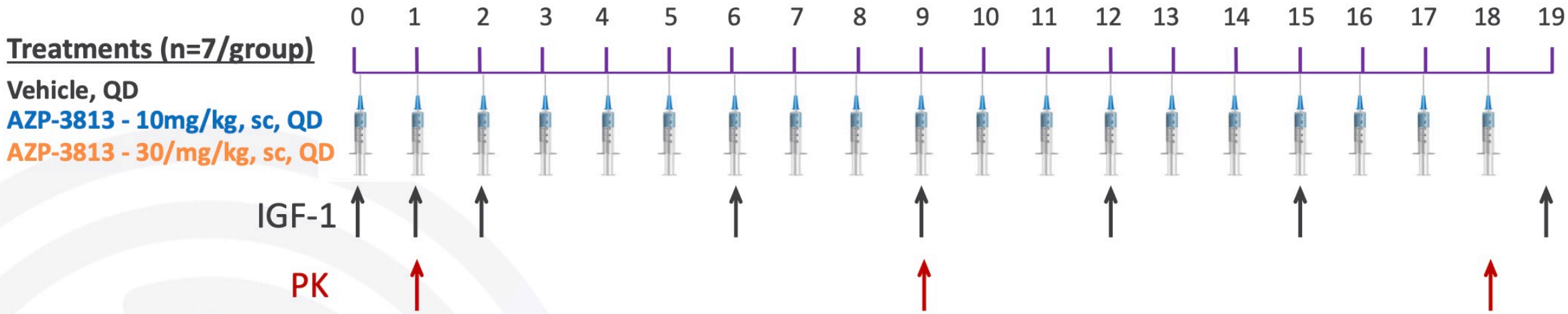
Study Design – Effect of Chronic QD Administration of AZP-3813 on IGF1 and Related Parameters in Juvenile Rats

Juvenile SD, CD rats (~5wk old, 150g at start of treatment) – rapidly growing



Key Goals:

- Maintenance of IGF-1 Suppression
- Pharmacokinetics with Continued Administration
- Examination of Anatomical Parameters

Day 19 – Termination:

- Comparative Photos
- Body Length (nose-anus)
- Femur Length + Photos
- Liver Weight - (Abs + %BW)

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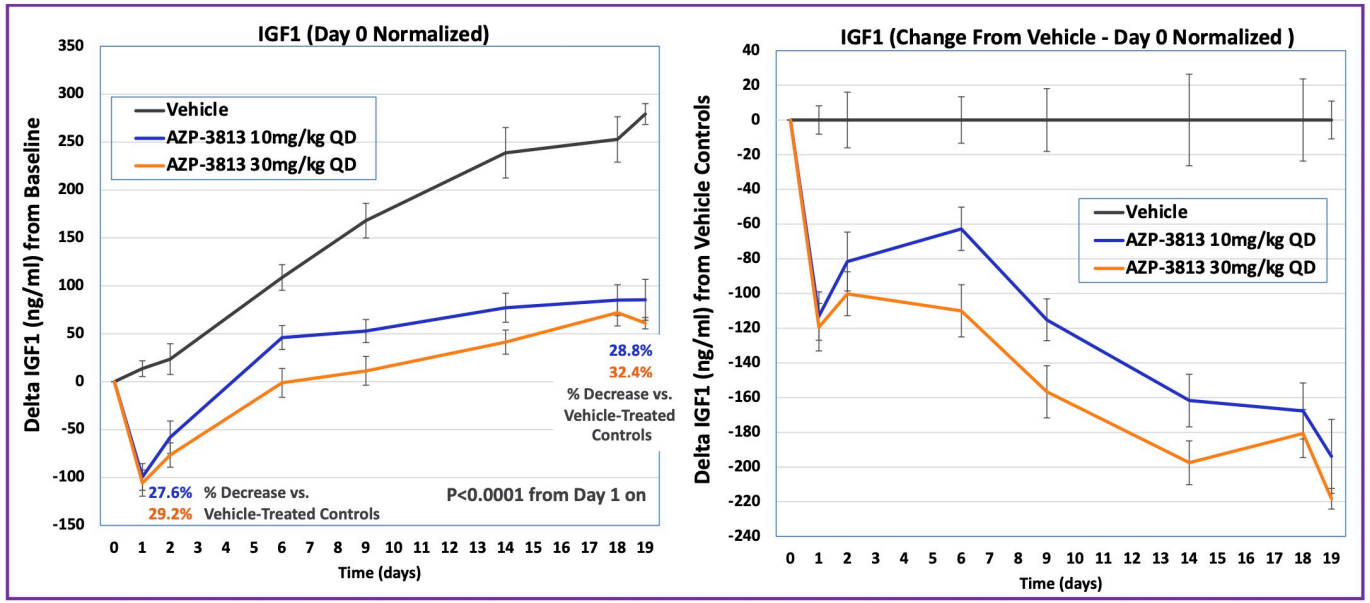
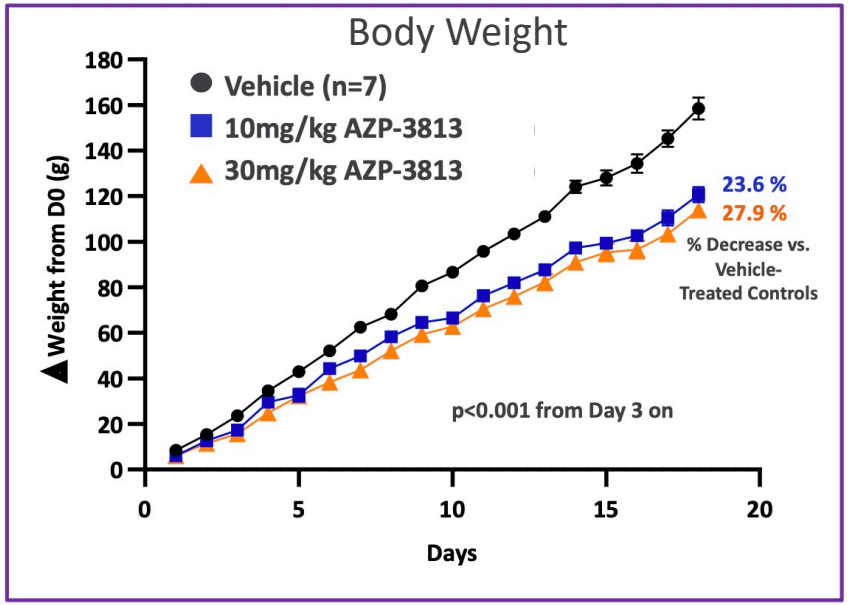
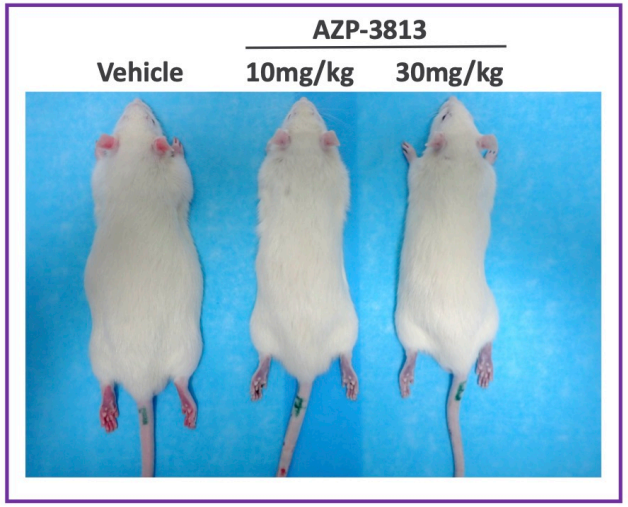
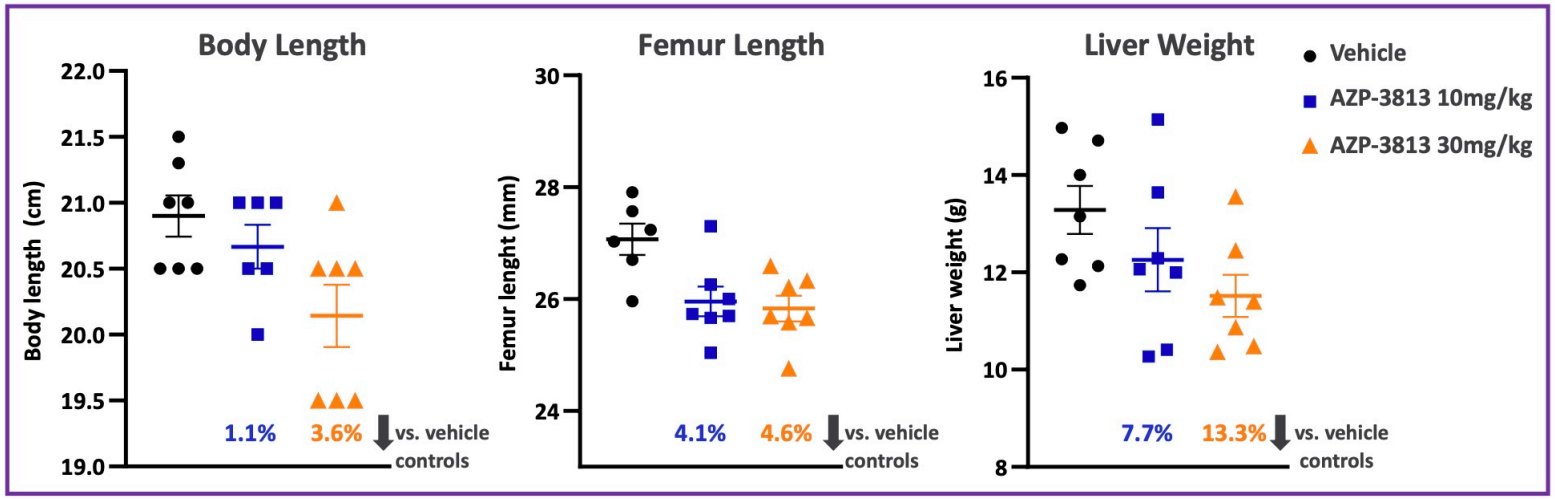
Rapid, Sustained Suppression of IGF1 and IGF1-Related Parameters with Continued, Daily Administration of AZP-3813









Summary and Conclusion

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 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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