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# A Phase 1 Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AZP-3813, a Novel, Small Peptide Growth Hormone Receptor Antagonist, in Healthy Subjects

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## INTRODUCTION

- Acromegaly is a rare, chronic endocrine disorder typically caused by the hypersecretion of GH from a benign tumor of the somatotroph cells of the pituitary, which, in-turn, stimulates the overproduction of IGF-1 from the liver.
- The goal in treating acromegaly is to normalize IGF-1 to alleviate the symptoms and manage potential medical complications caused by its excess.
- Treatment with somatostatin analog (SSA) monotherapy does not provide optimal control of circulating IGF-1 levels in most patients (1, 2).
- AZP-3813 is a novel, 16-amino acid peptide growth hormone receptor antagonism (GHRA), with an inherently long circulating half-life.
- AZP-3813 is being developed as add-on therapy for the treatment of acromegaly in patients insufficiently controlled with SSAs.
- Here, we report data from Phase 1 study to characterize the safety, tolerability, pharmacokinetics and pharmacodynamics of AZP-3813 in healthy subjects.

## MECHANISM OF ACTION

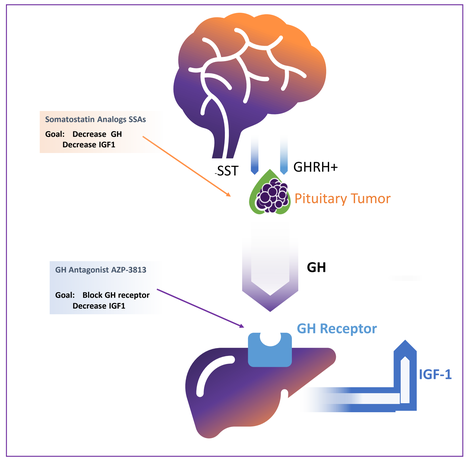


Fig.1 Additive effect of GHRA on SSAs.

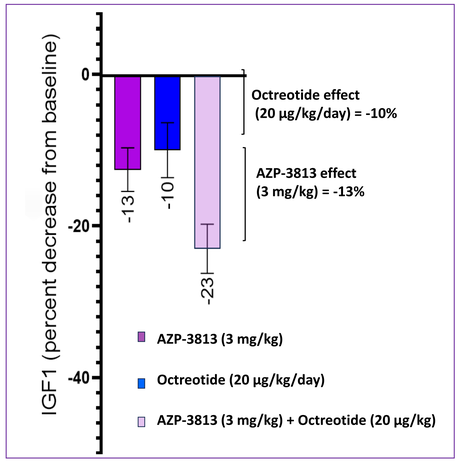


Fig.2 Additive effect of AZP-3813 when combined with octreotide on IGF-1 levels in normal rats. Data are mean of IGF-1 versus baseline + SEM (n=7/group).

- SSAs decrease GH and, consequently IGF-1.
- AZP-3813 binds to the GH receptor and blocks binding of GH.
- As a result there is reduced biological response and reduced stimulation of the liver to produce IGF-1 (Figure 1).
- AZP-3813 has demonstrated ability to decrease circulating levels of IGF-1 and an additive effect when combined with the SSA, Octreotide (20 µg/kg/day), in normal rats (3) (Figure 2).

## STUDY DESIGN AND SUBJECTS

- This was a randomized, double-blind, placebo-controlled single ascending dose (SAD) and multiple ascending dose (MAD) study conducted in a Phase 1 unit (ICON, Groningen, The Netherlands).
- Eligible healthy subjects included males and females of nonchildbearing potential aged 18 to 65 years with BMI of 19 to 28 kg/m$^2$ inclusive.
- Sequential cohorts were administered ascending doses of AZP-3813 or placebo by SC injection in the abdominal wall.

| | SAD | MAD |
|---|---|---|
| Dose | Single<br>3 to 120 mg | Once a day for 14 days<br>10 to 120 mg |
| N/cohort<br>(3 mg cohort) | 6 (3) AZP-3813<br>2 placebo | 6 AZP-3813<br>2 placebo |
| Total N | 53 (39 AZP-3813) | 48 (36 AZP-3813) |

## SAFETY AND TOLERABILITY

- Good tolerability with no safety concerns.
- No serious adverse event (SAE), or treatment-emergent adverse event (TEAE) leading to study discontinuation. All TEAEs reported were mild or moderate in severity.
- No clinically significant abnormalities with respect to safety labs, vital signs and ECG.

## PHARMACOKINETICS

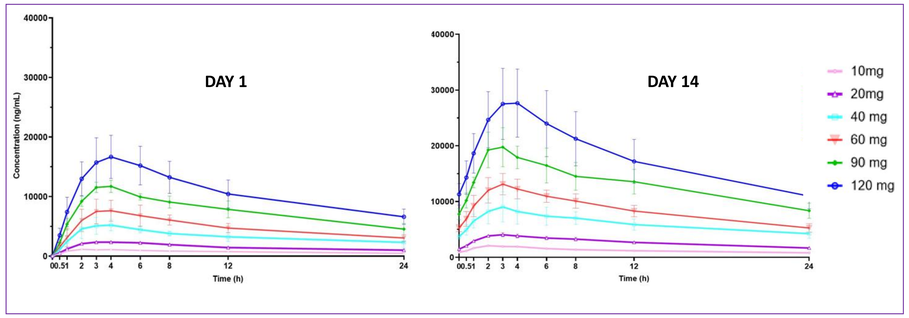


Fig.3 Mean (±SEM) plasma concentration versus time profile of AZP-3813 following single (Day 1) and repeated administration (Day 14).

- $C_{max}$ and AUC increased in a dose proportional manner.
- Half life ($t_{1/2}$) of AZP-3813 was 20-22 h consistent with QD (once a day) dosing.
- The accumulation ratio was 1.75.

## PHARMACODYNAMICS

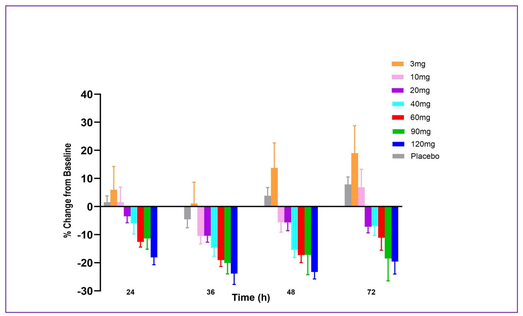


Fig.4 Mean % change in IGF-1 from baseline (± SE) following a single injection of AZP-3813 in the SAD portion of the study.

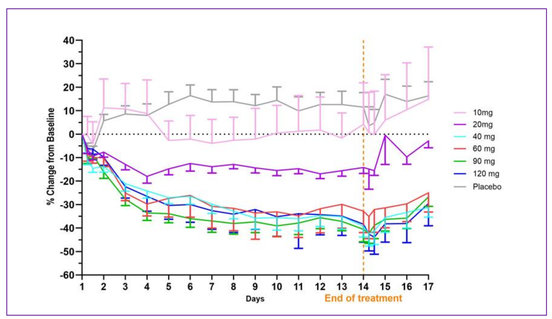


Fig.5 Mean % change in IGF-1 from baseline (± SE) following multiple daily doses of AZP-381 in the MAD portion of the study.

- In SAD, AZP-3813 induced a rapid dose related decrease in IGF-1 levels at doses of 10 mg and above with a more prolonged reduction at higher doses (up to 72 hours) (Figure 4).
- AZP-3813 administered for 14 days induced a gradual, sustained decrease in IGF-1 levels.
- The suppression of IGF-1 is greater after 14 days as compared to single administration at the same dose, consistent with a cumulative effect of repeated administration.
- Maximum % change from baseline adjusted to the placebo is approximately 50% (Figure 5).

## SUMMARY AND CONCLUSION

- Single and multiple administration of AZP-3813 for 14 days of AZP-3813 was well tolerated with no safety concerns.
- The half life ($t_{1/2}$) of AZP-3813 was estimated to be 20-22 hours.
- Repeated administration of AZP-3813 induced a dose related decrease in IGF-1 levels well within the level of reduction expected to result in excellent control of IGF-1 levels in patients with acromegaly.
- Collectively, the data support further testing in patients with acromegaly.

## REFERENCES

(1) Giustina A et al, Rev Endocr Metab Disord 2019;
(2) Giustina A et al, Pituitary 2024;
(3) Poster MON-110 Ravel et al, ENDO 2024.

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