Safety, Tolerability, Pharmacokinetics and Pharmacodynamics following Single and Multiple Administration of AZP-3601, a Novel Long-Acting PTH Analog, to Healthy Adults

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INTRODUCTION

- Hypoparathyroidism (HP) is a rare disease characterized by a deficiency in parathyroid hormone (PTH) that results in hypocalcemia, hyperphosphatemia, hypercalciuria and low bone turnover.
- Current treatment approaches (i.e., oral calcium, active vitamin D, rhPTH (1-84)) do not provide adequate or consistent control of either serum calcium or clinical symptoms over a full 24-hour period, resulting in reduced quality of life. In addition, hypercalciuria may be aggravated with oral calcium supplementation and is not corrected with rhPTH (1-84).
- AZP-3601, also known as LA-PTH, is a novel 36-amino-acid PTH analog that is being developed for the treatment of chronic HP.
- AZP-3601 was designed to potently and selectively bind to the R^0 conformation of the PTH1 receptor, which results in prolonged receptor signaling in vitro and prolonged calcemic responses in animals despite having a short circulating half-life (1,2).
- A Phase 1, double-blind, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) clinical trial has been conducted to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of AZP-3601 in healthy adults, and results are provided here.

AZP-3601

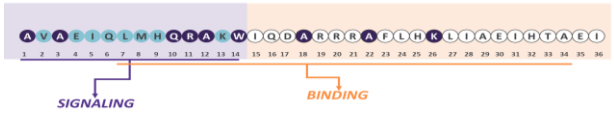

Fig.1 AZP-3601 is a synthetic 36-amino acid peptide. Sequence 1 to 14 and 15 to 36 are from natural PTH and PTHrP, respectively, with substituted amino acids indicated in solid purple.

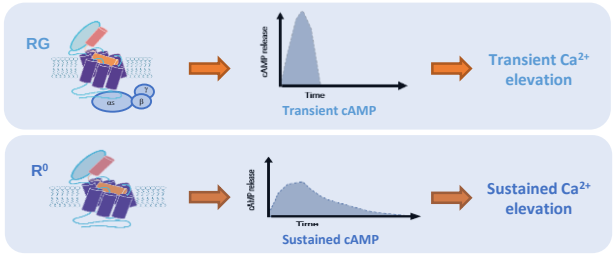

Fig.2 AZP-3601 has been designed to target the R^0 conformation of the PTH receptor in order to produce a sustained serum Ca elevation and to induce sustained Ca reabsorption by the kidney, despite having a short PK half-life. These properties also allow AZP-3601 to have a neutral impact on bone as has been demonstrated in multiple animal studies.

The PTH receptor (PTHR1) exists in two conformationally-distinct forms:

- RG, which rapidly releases the ligand once the G-protein is activated and released, ending its signal transduction, and resulting in a transient cAMP signal and transient calcium elevation.
- R^0, which allows continued association with the ligand and thereby multiple cycles of G-protein coupling and activation, resulting in a sustained cAMP signal and sustained calcium elevation (3).

PHASE 1 STUDY DESIGN

- Double-blind, placebo-controlled, SAD and MAD study conducted in a single Phase 1 unit (PRA Health Sciences, Groningen, The Netherlands).
- Sequential cohorts of healthy subjects aged 18-60 years with a body mass index of 19-28 kg/m² were administered ascending dose of AZP-3601 or placebo by subcutaneous injection in the abdominal wall.

	SAD	MAD
Dose	Single dose 5 to 120 µg	Once a day for 14 days 10 to 80 µg/day
N/cohort (5 µg cohort)	6 (4) AZP-3601 2 (1) Placebo	8 AZP-3601 2 Placebo
Total N	52 (39 AZP-3601)	50 (40 AZP-3601)

ALBUMIN-ADJUSTED SERUM CALCIUM

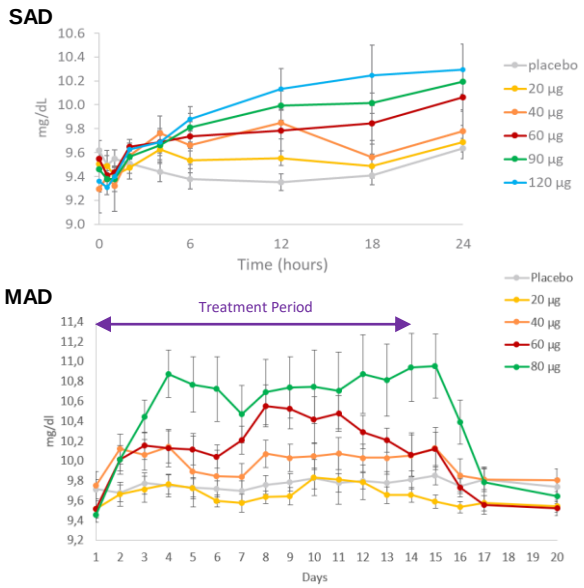

Fig.4 Albumin-adjusted serum calcium following a single and repeat administration for 14 days of AZP-3601. Data are means ± SEM. There was a dose dependent increase in mean albumin-adjusted serum calcium vs. placebo that was sustained over time, as expected from the mechanism of action. In SAD, the increase was sustained for up to 24 hours at 40 and 60 µg and up to 48 hours at 90 and 120 µg. In MAD, the effect was maintained up to 24 hours following last dose.

SAFETY AND TOLERABILITY

- Overall good tolerability with no safety concerns.
- No severe nor serious adverse events.
- Most frequent adverse events were typical of increases in serum calcium (eg., nausea, headache, somnolence) and were observed with dose dependent incidence and severity.
- In SAD, these AEs were observed at the highest doses (60, 90, 120 µg). As no hypercalcemia was noted, they were considered to be related to the speed in the rise of calcium.
- In MAD, these AEs were observed at 40 µg and higher and were more pronounced in 2 subjects at 60 µg, resulting in one drop-out.
- In both SAD and MAD, no post-dose changes of clinical relevance were observed in safety labs, ECG and blood pressure.

SERUM ENDOGENOUS PTH

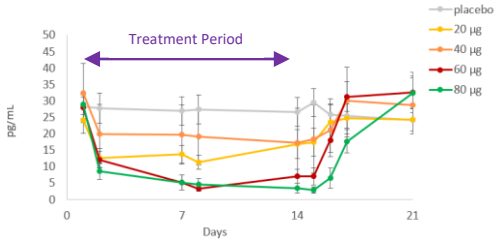

Fig.5 Serum endogenous PTH following repeat administration for 14 days of AZP-3601. Data are means ± SEM. There was a rapid dose-dependent decrease in serum endogenous PTH, consistent with the rise in serum calcium. PTH remained suppressed throughout the treatment period.

URINARY CALCIUM

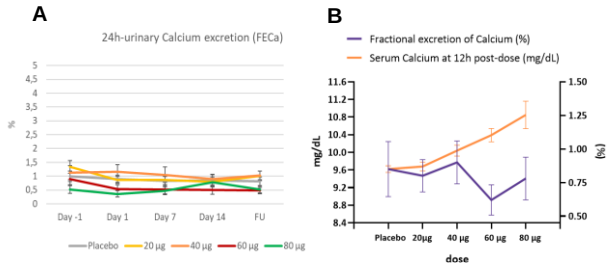

Fig 6. Urinary calcium excretion following repeat administration for 14 days of AZP-3601. Fractional excretion of calcium (FECa) was calculated using 24-hour urine calcium and fasting predose calcium values. Data are means ± SEM. No increase in FECa (A and B) despite marked elevation of albumin-adjusted serum calcium (B) at doses up to 60 µg. At 80 µg, the increase in the mean value is largely due to 1 patient who had increased urinary calcium associated with frank hypercalcemia (albumin-adjusted serum calcium>12 mg/dL on Day 5 to 14).

PHARMACOKINETICS

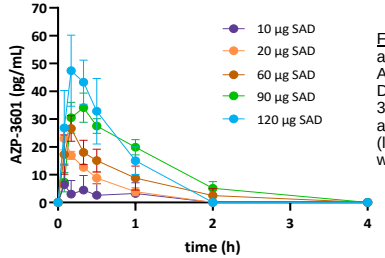

Fig.3 Pharmacokinetic profile after a single administration of AZP-3601 to healthy adults. Data are means ± SEM. AZP-3601 has a rapid absorption and a short elimination half-life (less than 1 hour), consistent with animal data.

BONE TURNOVER MARKERS

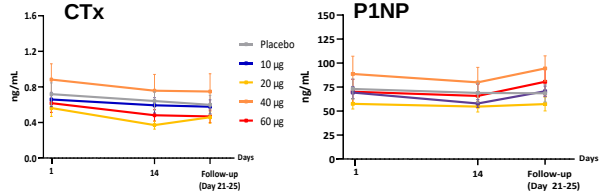

Fig.7 Serum bone biomarkers following repeat administration for 14 days of AZP-3601. Data are means ± SEM. No relevant changes were observed in bone resorption marker CTx and bone formation marker P1NP at any dose, reflecting a neutral effect on bone turnover during the 14 days treatment period.

SUMMARY AND CONCLUSION

- AZP-3601 is a novel, synthetic, 36-amino-acid peptide analog of human PTH that potently binds the R^0 conformation of the PTH1 receptor while maintaining a very short circulating half-life.
- Daily administration of AZP-3601 for 14 days to healthy adults induced a dose-dependent long-acting pharmacodynamic effect at doses of 20 µg and above.
- There was a rapid onset of increase in serum calcium that was sustained throughout the treatment period and maintained up to 24 hours post last dose.
- The effect was associated with a dose-dependent decrease in endogenous PTH.
- No increase in urinary calcium was observed despite the marked rise in serum calcium, suggesting sustained calcium reabsorption by the kidney.
- No significant changes in bone turnover markers were noted, reflecting a neutral effect on bone turnover, as expected based on mechanism of action.
- Taken together, these data support further testing of AZP-3601 in patients with chronic hypoparathyroidism. A multi-center, 3-month multiple ascending dose trial in patients with chronic hypoparathyroidism is currently ongoing.

REFERENCES

1. Bi R, and al. JBMR 2016. 2. Shimizu M, et al. JBMR 2016. 3.Gardella T, et al. Pharmacol Rev 2015.