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, hypouricemia and bone turnover.
- Current treatment approaches (i.e., oral calcium, active vitamin D, and PTH analogs) 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, hypercalcemia may be aggravated with oral calcium supplementation and is not corrected with PTH administration.
- AZP-3601, also known as LA-PTH, is a novel 36-amino-acid PTH analog that is currently being developed for the treatment of chronic HP.
- AZP-3601 was designed to potently and selectively bind to the PTH1 receptor, which results in prolonged receptor signaling in vitro and prolonged calcemic responses in animals despite a short circulating half-life (11.2 h).
- 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.

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.

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 (e.g., 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 lab, ECG and blood pressure.

SERUM ENDOCRINOPHAGE

Data suggest that AZP-3601 is a novel, synthetic, 36-amino-acid peptide analog of human PTH that potently binds the PTH1 receptor 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-PTH.
- 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 hyperparathyroidism. A multi-center, 3-month multiple ascending dose trial in patients with chronic hyperparathyroidism is currently ongoing.

SUMMARY AND CONCLUSION

- AZP-3601 is a novel, synthetic, 36-amino-acid peptide analog of human PTH that potently binds the PTH1 receptor of the PTH1 receptor while maintaining a very short circulating half-life.
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DATA

- 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.

REFERENCES