A Single Administration of AZP-3601, a Novel, Long-Acting PTH Analog, Induces a Significant and Sustained Calcemic Response: Preliminary Data From a Randomized, Double-Blind, Placebo-Controlled Phase 1 Study

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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.
- HP manifestations vary from mild to debilitating symptoms and reflect impact on a large number of tissues and organs including the muscles, brain, heart, and the kidney.
- Hypercalciuria is of particular concern in HP as it may lead to impaired renal function in the long-term.
- 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 supplement and is not corrected with rhPTH (1-84).
- AZP-3601, also known as LA-PTH, is a novel PTH analog being developed for the treatment of HP.
- In animals, AZP-3601 induced prolonged pharmacodynamic effect on serum calcium following single and multiple administrations (1,2), despite a short circulating half-life.

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.

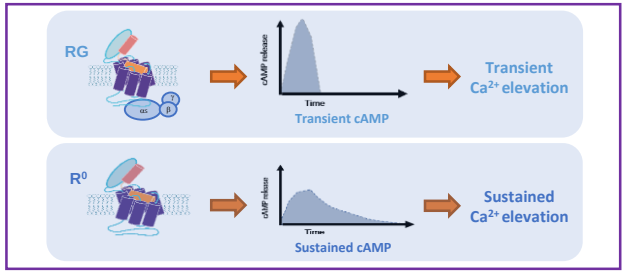

Fig.2 AZP-3601 has been designed to target the R^0 conformation of the PTH receptor in order to produce a sustained serum Ca elevation and to induce sustained Ca reabsorption by the kidney. AZP-3601 has a short PK half-life which is intended to prevent prolonged exposure to RG and associated adverse effects on bone, in particular bone resorption.

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)

BINDING of AZP-3601 to PTHR1

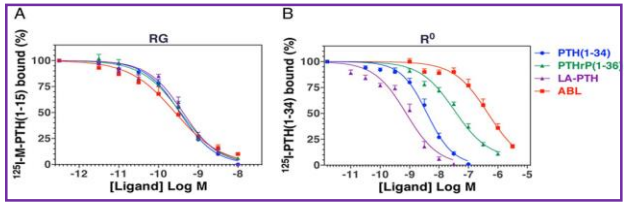

Fig.3 Ligand Binding to the RG (A) and R^0 (B) conformation of PTHR1

Binding was assessed by competition methods in membranes prepared from GP-2.3 cells stably expressing PTHRP1. LA-PTH = AZP-3601. ABL= Abaloparatide (PTHrP (1-34) analog). Data are means ± SEM (4). AZP-3601 showed enhanced binding to the R^0 conformation as compared with other PTH analogs.

PHARMACOKINETICS & PHARMACODYNAMICS IN ANIMALS

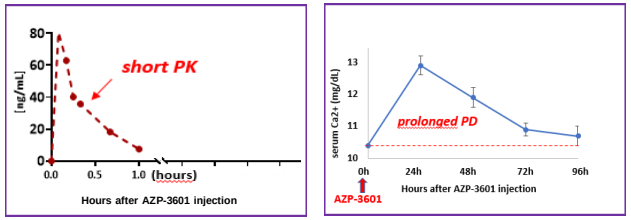

Fig.4 Effects of single-dose administration of AZP-3601 on sCa levels in normal monkeys (2)

Cynomolgus monkeys were injected SC with 2µg/kg AZP-3601. Blood samples were collected at the time indicated from the saphenous vein and assessed for serum calcium. Data are means ±SEM. AZP-3601 induced a prolonged PD while having a short half-life.

PHASE 1 SUBJECTS AND METHODS

- A double-blind, placebo-controlled, single and multiple ascending dose study currently ongoing in a single Phase 1 unit (PRA Health Sciences, Groningen, The Netherlands).
- The study protocol has been approved by the national competent authority and the Independent Ethics Committee (IEC).
- The Single Ascending Dose (SAD) part consists of sequential cohorts of 4 (cohort 1) to 8 (subsequent cohorts) healthy male subjects aged 18-60 years, with a body mass index of 19-28 kg/m².
- Subjects receive AZP-3601 or placebo at a ratio of 3:1. The study drug is administered in the morning by subcutaneous injection in the abdominal wall.
- For dose escalation, review is performed following completion of each cohort by a study Safety Review Committee (SRC) based on safety and tolerability data, as well as on selected pharmacodynamic data, including albumin-adjusted serum calcium and endogenous serum PTH. These selected data are unblinded at the group level only at the time of SRC review, in order to guide dose escalation and remain blinded at the subject level until database lock (DBL).
- Serum calcium and PTH data that have been used for dose escalation decisions for the initial 4 cohorts are presented here. These data will be subject to a closing audit check before DBL and before being considered as final data.

SINGLE ASCENDING DOSE PHARMACODYNAMICS

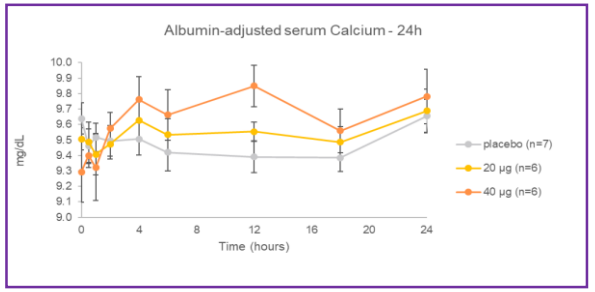

Fig.5. Albumin-adjusted serum calcium following a single administration of AZP-3601.

Serum samples have been collected at pre-dose, and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours following dosing and data are presented as means.

N=7 for placebo, N=6 for AZP-3601 treated groups.

There is a clear dose-dependent increase in mean albumin-adjusted serum calcium vs placebo following a single administration of AZP-3601. At 40 µg, the increase was clinically significant (mean peak change vs placebo at 12hrs: 0.81 mg/dl) and sustained for up to 24 hours post-administration (mean change vs placebo at 24hrs: 0.47 mg/dl).

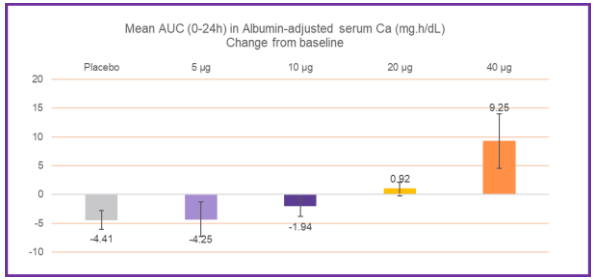

Fig.6. Change from baseline in albumin-adjusted serum calcium over 24 hours following a single administration of AZP-3601.

Data are presented as mean area under the curve (AUC) ± SEM. N=7 for placebo, N=6 for AZP-3601 treated groups.

The normal physiological diurnal variation of albumin-adjusted serum calcium (as seen for the placebo group in Fig.5 was gradually attenuated with 5 and 10 µg AZP-3601, and was completely eliminated with 20 µg. With the dose of 40 µg AZP-3601, mean albumin-adjusted serum calcium values were significantly increased but stayed within normal laboratory range and remained elevated through at least 24 hours post-administration.

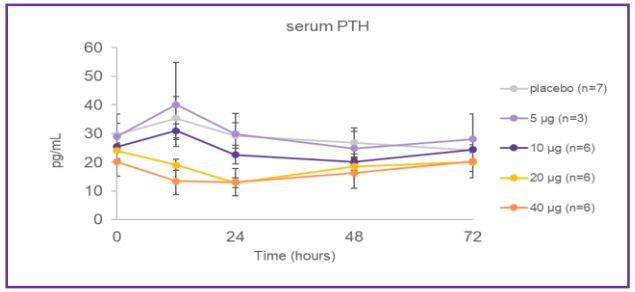

Fig.7. Endogenous serum PTH (1-84) following a single administration of AZP-3601.

Serum samples have been collected at pre-dose, and at 12 and 24 hours following dosing and data are presented as means. N=7 for placebo, N=6 for AZP-treated groups.

There is a clear decrease in endogenous serum PTH at 20 and 40 µg consistent with the calcium data. At 40 µg, the decrease seems to persist up to 48 hours post-dose.

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 having a very short circulating half-life.
- These data provide initial evidence of the pharmacodynamic effect of AZP-3601 in healthy humans with a sustained calcemic response over 24 hours following a single administration and support further dose escalation.
- Final and full analyses of this Phase 1 study will be provided at a later date.

REFERENCES

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DISCLOSURES

SA, MO, MDC and CG are currently employees of Amolyt Pharma. JW is principal investigator of the study and is currently employed by PRA. MM is advisor on the study and receives an honorarium from Amolyt Pharma.

ACKNOWLEDGEMENTS

The study has been sponsored by Amolyt Pharma.

Poster presented at ENDO 2021, March 20-23 [Virtual]