Safety, Tolerability and Pharmacodynamics of AZP-3601, a Novel Long-Acting PTH Analog, in Healthy Adults: Data From a Randomized, Double-Blind, Placebo-Controlled Phase 1 Study

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Introduction

• Hypoparathyroidism is a rare disease characterized by a deficiency in parathyroid hormone that results in hypocalcemia, hyperphosphatemia, hypercalciuria and low bone turnover.

• Hypercalciuria is of particular concern 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 supplementation, and is not corrected with rhPTH (1-84).
AZP-3601, also known as Long-Acting PTH (LA-PTH), is a novel PTH analog being developed for the treatment of HP.

AZP-3601 is a synthetic 36-amino acid peptide that contains sequences of both human PTH and PTHrP, with several conservative amino acid substitutions.
AZP-3601 Mechanism of Action

- AZP-3601 has been designed to target the R\(^0\) conformation of the PTH receptor in order to produce a sustained serum calcium elevation and to induce sustained calcium 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.
Pharmacokinetics and Pharmacodynamics in Animals

In normal monkeys, AZP-3601 induced a prolonged calcemic response following a single administration while having a short half-life.

Adapted from Shimizu M et al., JBMR, 2016 & unpublished PK data
Phase 1 Subjects and Methods

- Double-blind, placebo-controlled, single and multiple ascending dose study currently ongoing in a single Phase 1 unit
- Single Ascending Dose (SAD) part completed
  - Sequential cohorts of healthy subjects aged 18-60 years
  - Sc injection of AZP-3601 at a dose of up 120 µg or placebo (ratio of 3:1)
- Data review performed following each cohort by a Safety Review Committee, PD data were unblinded at the group level to guide dose escalation
Data are presented as mean ± SEM

• Dose-dependent increase in mean albumin-adjusted serum calcium vs placebo following a single administration of AZP-3601.
• The increase was sustained for up to 24 hours post-administration at 40 and 60 µg and for up to 48 hours at 90 and 120 µg
Single Ascending Dose Pharmacodynamics

Data are presented as mean ± SEM

- Dose-dependent decrease in mean endogenous serum PTH consistent with the calcium data
- Mean values remained lower at the highest doses up to 72 hours post-dose
- Endogenous serum PTH was inversely correlated with serum calcium
Summary and Conclusions

• AZP-3601 is a novel, synthetic, 36-amino acid peptide analog of human PTH that preferentially and potently binds the R\(^0\) conformation of the PTH1 receptor resulting in a prolonged and sustained calcemic response, while having a very short circulating half-life.

• These initial data from a Phase 1 trial in healthy volunteers demonstrated the expected pharmacodynamic effect of AZP-3601 with a sustained calcemic response over at least 24 hours following a single administration.

• AZP-3601 is currently being tested in a 14-day Multiple Ascending Dose study in healthy volunteers.

• Final and full analyses of this Phase 1 study will be provided at a later date.
Thank you for your attention!

Place de la baleine, Lyon