OC12.2
Improved Glucose Metabolism and Decreased Weight Gain in Leptin-Resistant, IGFBP2-Deficient, db/db Mice Induced by AZP-3404, a 9-Amino Acid of IGFBP2

Michael D. Culler¹, Stéphane Milano¹, Michel Ovize¹, Thomas Delale¹, Aart Jan van der Lely², David Clemmons³

¹Amolyt Pharma, Cambridge, MA, USA and Ecully, France. ²Erasmus University MC, Rotterdam, Netherlands. ³New Paradigm Therapeutics, Chapel Hill, NC, USA
Disclosures

Nothing to Disclose
Metabolic effects of leptin mediated by IGFBP-2

Adipocytes

Hypothalamus

Liver

Skeletal Muscle

LEPTIN

IGFBP-2

Insulin-like Growth Factor-Binding Protein 2 (IGFBP-2)

Glucose control / Insulin sensitivity

Builds trabecular bone

Decreases fat

Decreases appetite


Xi G et al. J Bone Miner Res. 29:2427 (2014)
Xi G et al. J Bone Miner Res. 31:1300 (2016)
HBD-1-derived peptide, AZP-3404, reproduces the metabolic activity of IGFBP-2

**IGFBP-2**

- 325 Amino Acid Protein
  - IGF-1 binding not required for metabolic activity

**AZP-3404**

- 9 AA acylated peptide
- Enzymatically stable
- Enhanced PK

Dose-related increase in glucose uptake by mouse muscle cells

Independently reproduces metabolic activity of IGFBP-2 on adipose, glucose metabolism and bone
db/db mouse – Leptin produced, but defective leptin receptor

leptin-resistant = IGFBP-2 deficient

Hypothesis:

Leptin → Skeletal Muscle Adipose → IGFBP2

Dysfunctional Leptin Receptor/Transduction

AZP-3404

Adipose Inhibition

Glucose Homeostasis

Bone Maturation

Plasma Leptin (ng/mL)

obese
Insulin-resistant
hyperglycemia
hyperinsulinemia

Hall et al., 2014
Geng et al., 2019

CONFIDENTIAL
Study Plan

6wk old db/db mice (n=10/group) → Weekly Body Weight / Food Intake → 8 Weeks Treatment with AZP-3404 (1, 3 and 6mg/kg) or Vehicle, sc, BID → 8 Wk ipGTT → Fasting Insulin HOMA Index

7 Day Pre-Trt / Wt → Group Randomization → 4 Wk ipGTT
Body weight gain over 8 weeks of treatment

MRI analysis revealed that the decrease in weight gain was due to decreased fat mass, largely visceral, without impact on lean mass.

**** p<0.0001
*** p<0.001
* p<0.05 versus Vehicle

**Weekly Change in Weight Gain (Wk 0 Normalized)**

**8 Wk Change in BW Gain from Vehicle**

- Vehicle
- AZP-3404 1mg/kg
- AZP-3404 3mg/kg
- AZP-3404 6mg/kg
4-Week ipGTT - Highest dose increases glucose disposal

4 Wk ipGTT – Change from Baseline

4 Wk ipGTT - Change from Vehicle

AUC (mg/dL.min)

Vehicle
AZP 1mg/kg
AZP 3mg/kg
AZP 6mg/kg

* p<0.006
8-Week ipGTT - All doses increase glucose disposal

8 Wk ipGTT - Change from Baseline

8 Wk ipGTT - Change from Vehicle

*\( p < 0.05 \)
8-Week treatment - All doses decrease fasted insulin level and HOMA-IR

HOMA IR in vehicle-treated animals consistent with literature values for db/db mice
Leptin-resistant, IGFBP2-deficient, db/db mice treated with AZP-3404 displayed:

- A progressive decrease in the rate of body weight gain
  - Due to decreased fat mass, largely visceral, *without* impact on lean mass
- Significantly increased glucose disposal following a glucose challenge
- Decreased fasted insulin levels and improved insulin sensitivity (decrease in the HOMA insulin-resistance score)

The present results demonstrate that AZP-3404 reproduces the weight- and glucose-modulating action of IGFBP-2, and may have potential for therapeutic use in syndromes characterized by insulin resistance and/or obesity
Thank you!