

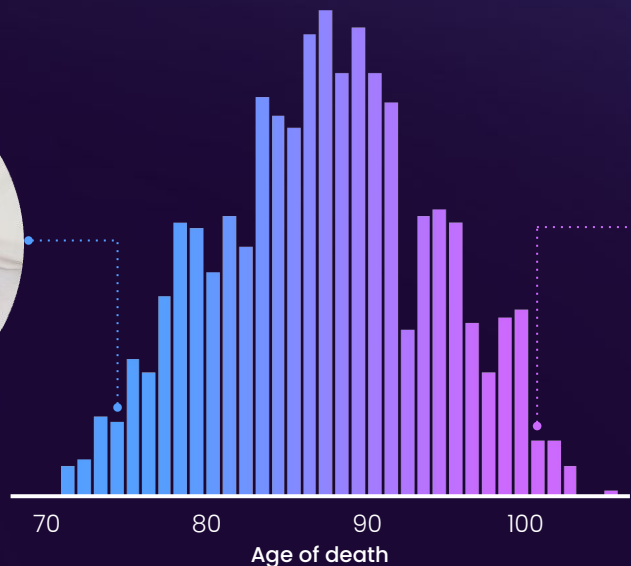
The Apelin Receptor Agonist Azelafrag Reduces Weight Gain & Improves Body Composition in Diet-Induced Obese Mice

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ObesityWeek
November 6, 2024

We know there are many pathways that impact human lifespan and metabolic health; it is our mission to find them and develop therapeutics to target them



A 50+ year natural human experiment

50M+

Molecular data points

10K+

Profiles generated

50+

Years of follow-up

Detailed healthspan trajectories



Physical function

- Grip strength
- Walking speed
- Mobility



Metabolism

- BMI
- Skinfold thickness
- Waist / hip circumference

The BioAge platform: Apelin signaling impacts muscle & metabolism

Target ID

Target validation

Discovery & development



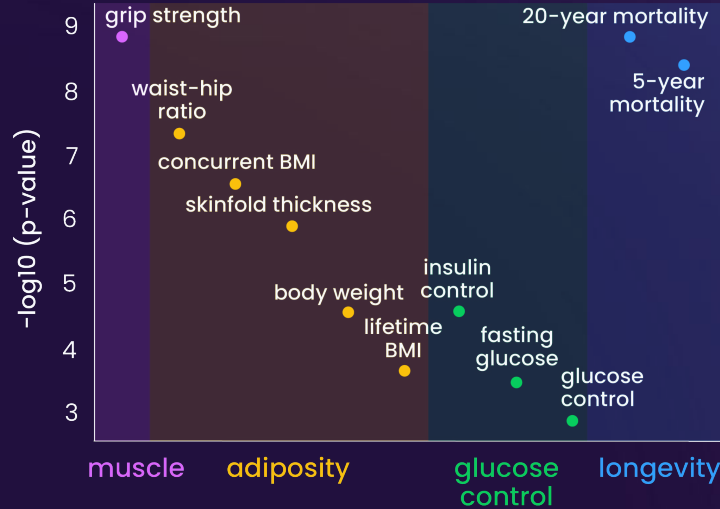
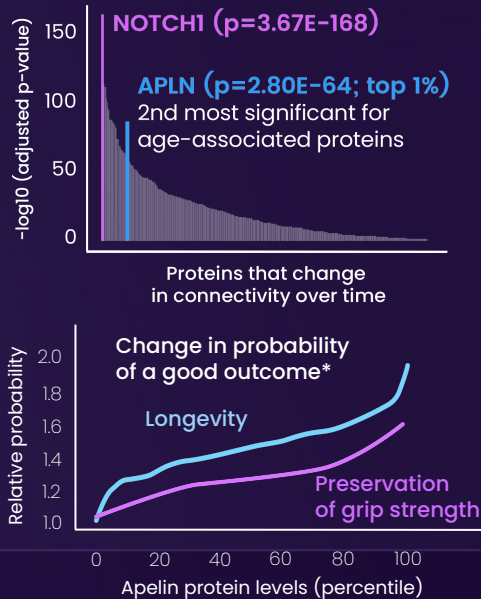
Apelin pathway shows strong signal in human data



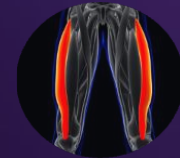
APJ agonist azelaprag showed functional and metabolic benefits in vivo



APJ agonist azelaprag showed muscle and metabolic benefits in Ph1b



Licensed from Amgen



Improvements shown in:

- Muscle dimensions
- Metabolism
- Muscle quality

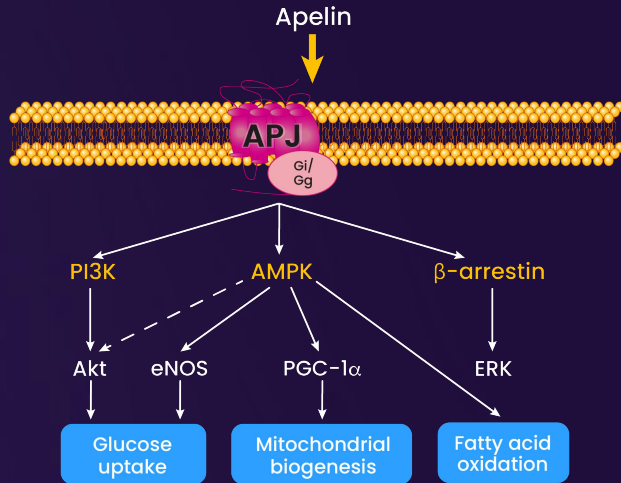
Ph1b trial in healthy elderly volunteers on bed rest

Apelin is an exerkin and mimics many benefits of exercise

Shared biology between apelin & exercise



Exercise stimulates release of apelin into circulation



Systemic benefits

- ↑ Balance of lean & fat mass
- ↑ Basal metabolic rate
- ↑ Protein synthesis
- ↑ Mitochondrial biogenesis
- ↑ Insulin sensitivity / glucose metabolism



Among complementary oral mechanisms, exercise mimetics like azelaprag have the greatest potential to address key unmet needs

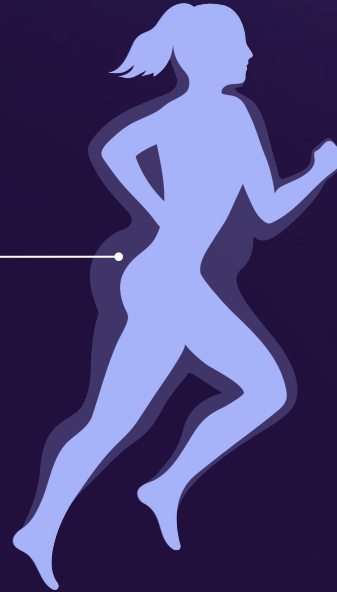
Exercise mimetics for obesity

Benefits of targeting exercise

- ✓ Safe way to increase energy expenditure
- ✓ Highly translational benefits

Key potential clinical value propositions

- ✓ Increased oral weight loss
- ✓ Improved body composition
- ✓ Improved tolerability



Therapeutic approach

Incretins + exercise mimetic



Potential pharmacological
parallel to diet
and exercise

Azelaprag showed significant muscle & metabolic benefits and was well tolerated in a Ph1b study of older subjects on bed rest

Ph1b design



10 days of bed rest & dosing

Healthy subjects 65+
(N=10 placebo,
N=11 azelaprag)

Azelaprag (240mg) or
placebo via daily IV
infusion

Double-blind,
non-randomized

Muscle size

Thigh circumference



Circumference

$p < 0.001$

Muscle size
(Vastus lateralis)



Diameter
(thickness)

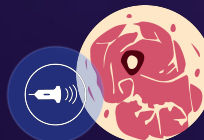
$p < 0.01$

Cross-sectional area

$p < 0.05$

Fat infiltration

Muscle degeneration

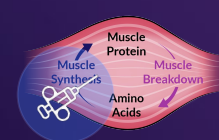


Muscle grade (progression)

$p < 0.005$

Metabolism

Muscle protein synthetic rate



Cumulative protein synthesis

$p < 0.005$

Clinical multi-omics: Predicted metabolic effects consistent with role as exerkinase

Serum proteomics



Resting energy expenditure



Cardiorespiratory fitness: VO_2 max

Single-nucleus transcriptomics



↑ Oxidative metabolism
↑ Glucose control



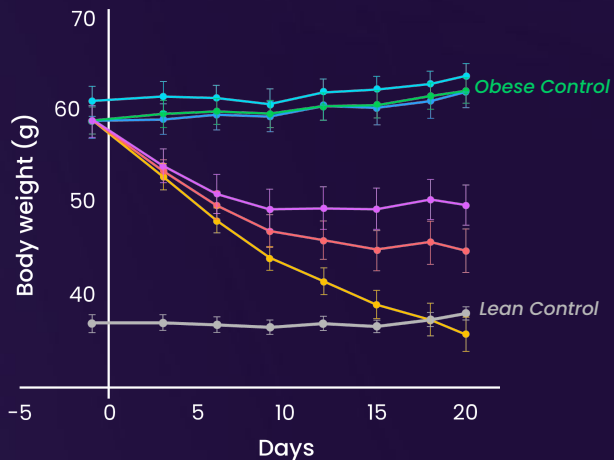
↑ Lipid metabolism

Azelaprag increased overall weight loss with tirzepatide to ~40%; similar results observed with semaglutide suggest a class effect

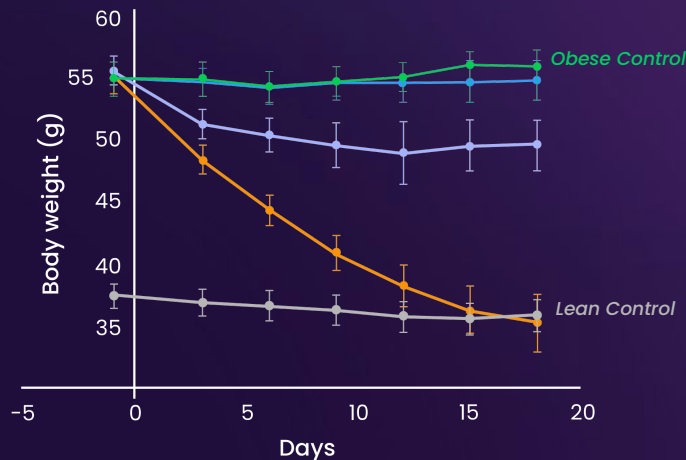


Overall weight loss

Tirzepatide



Semaglutide

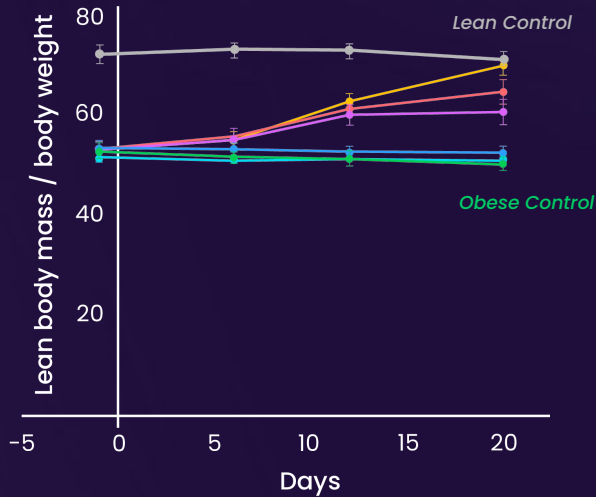


- Lean Control
 Azelaprag (0.275g/L)
 Tirzepatide (10nmol/kg)
 Tirzepatide (10nmol/kg) + Azelaprag (0.275g/L)
 Semaglutide (30nmol/kg)
- Vehicle
 Azelaprag (1.1g/L)
 Tirzepatide (10nmol/kg) + Azelaprag (1.1g/L)
 Semaglutide (30nmol/kg) + Azelaprag (1.1g/L)

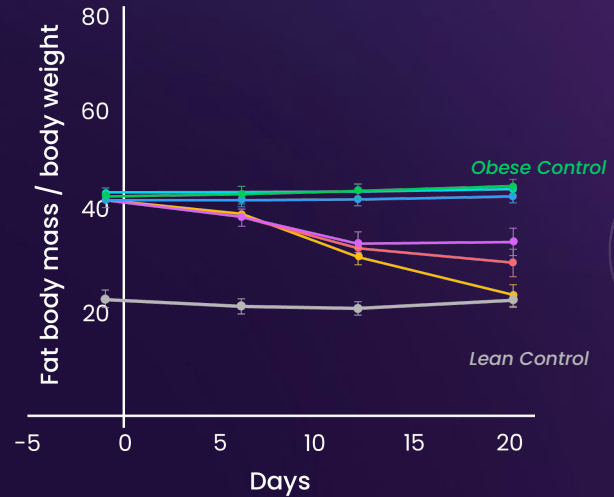
Addition of azelaprag to tirzepatide restored body composition to that of lean controls in a dose-dependent fashion



% Lean Mass by EchoMRI



% Fat Mass by EchoMRI



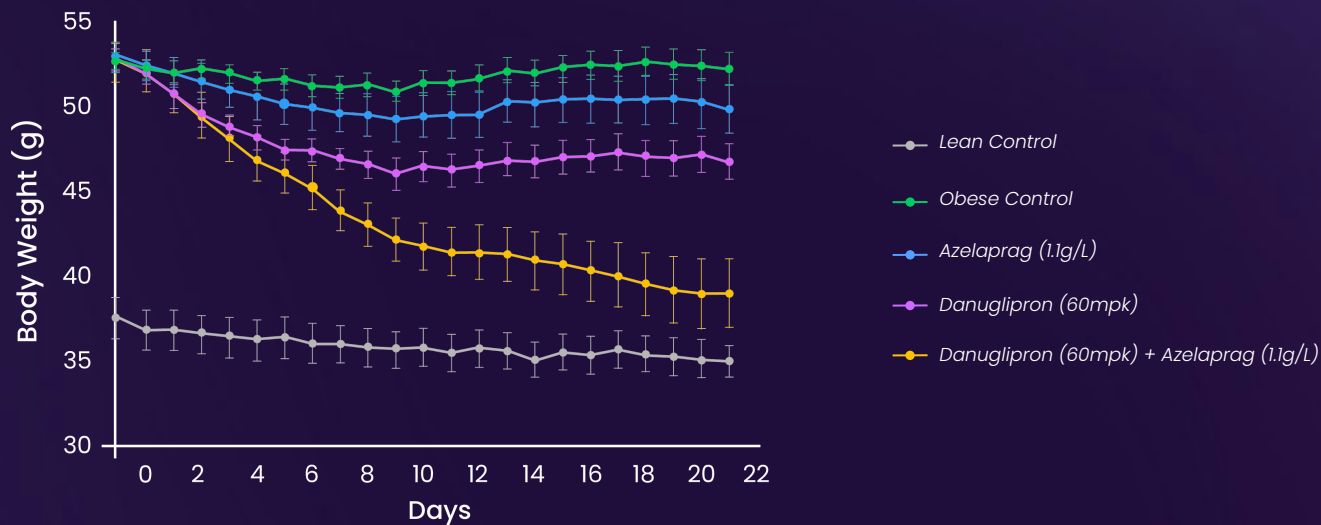
- Lean Control
- Azelaprag (0.275g/L)
- Tirzepatide (10nmol/kg)
- Tirzepatide (10nmol/kg)+ Azelaprag (1.1g/L)
- Vehicle
- Azelaprag (1.1g/L)
- Tirzepatide (10nmol/kg)+ Azelaprag (0.275g/L)

Note: Mice in all groups lose both lean mass and fat mass; with Azelaprag, lean body composition (% lean mass) is restored

Azelaprag also increased overall weight loss with oral GLP-1R agonist danuglipron in obese hGLP-1R mice



Overall weight loss

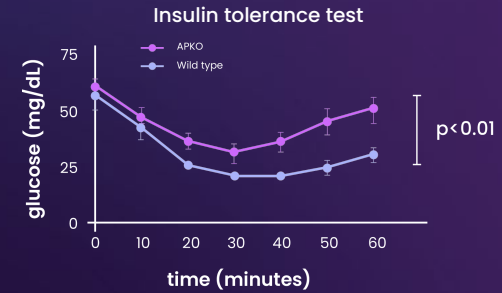
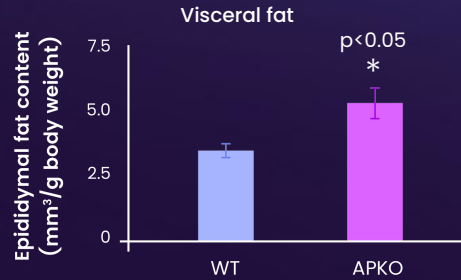


Note: Experiment performed in obese hGLP-1R mice. Danuglipron was dosed PO QD; azelaprag was dosed in the drinking water.

Apelin genetics reinforce beneficial role in systemic metabolism

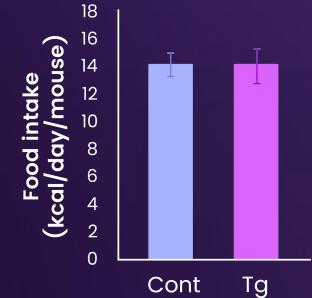
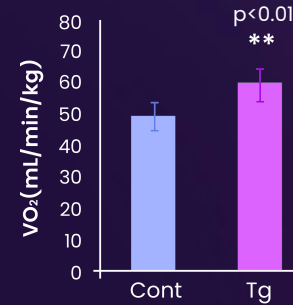
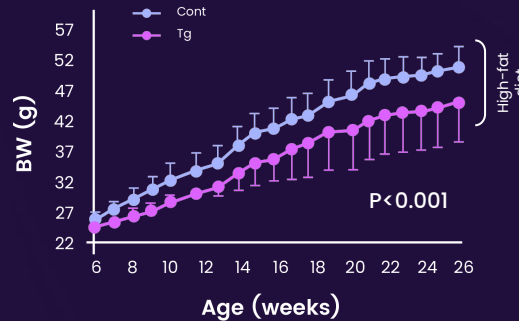
Apelin KO

- ↑ adiposity
- ↑ insulin resistance



Apelin transgenic

- ↓ weight gain on high fat diet
- ↑ Basal metabolic rate
- No impact on energy intake



Consistent genetic evidence in humans:

Genome-wide significant associations for the apelin receptor APJ include BMI, lean mass, and serum lipids

Study 1: Azelaprag monotherapy in mice on a high-fat diet



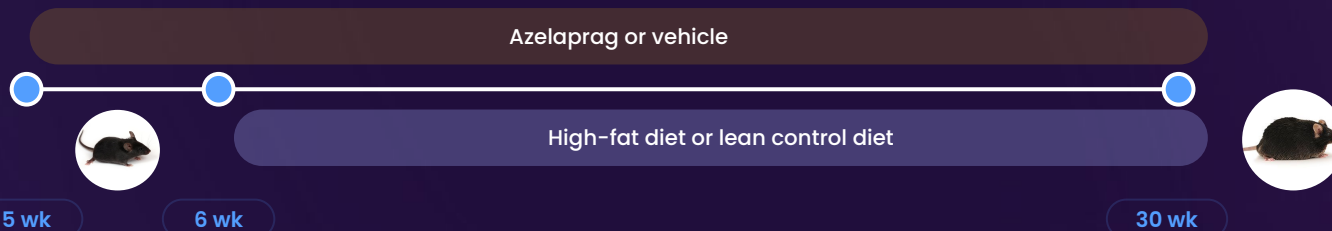
Arms (n=15-16 mice per arm)

- Lean control diet
- High-fat diet (HFD)
- High-fat diet + azelaprag (3.3 g/L in drinking water)

Measurements

- Body weight
- Body composition
- Food / water intake
- Liver enzymes and free fatty acids

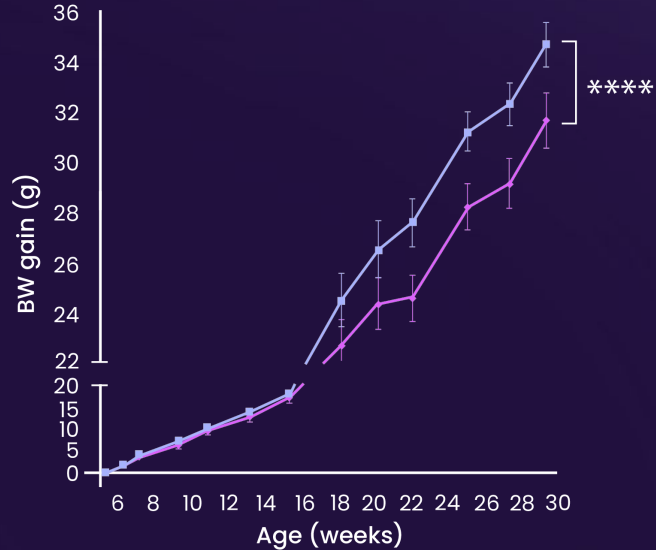
Timeline





Azelaprag reduced weight gain on a high-fat diet, recapitulating mouse genetics

Body Weight Gain

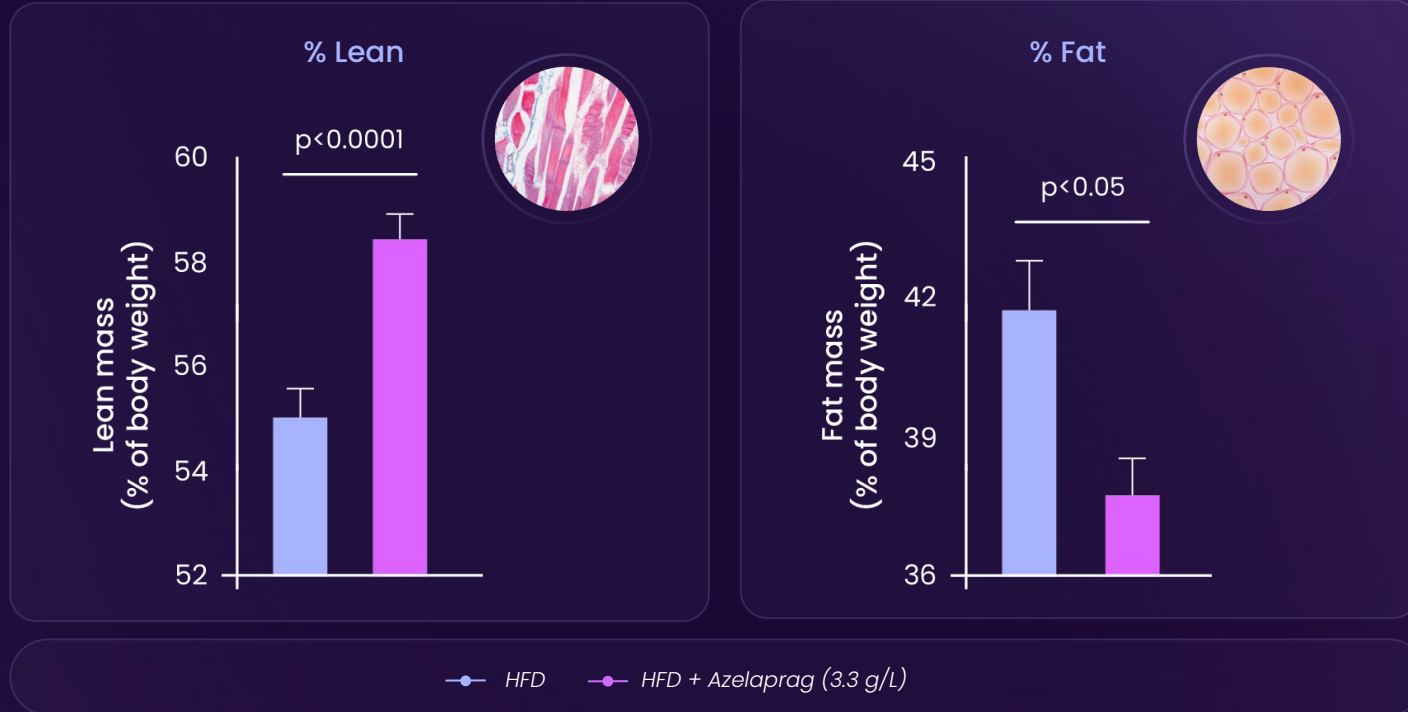


—●— HFD —●— HFD + Azelaprag (3.3 g/L)



Azelaprag improved body composition on a high-fat diet

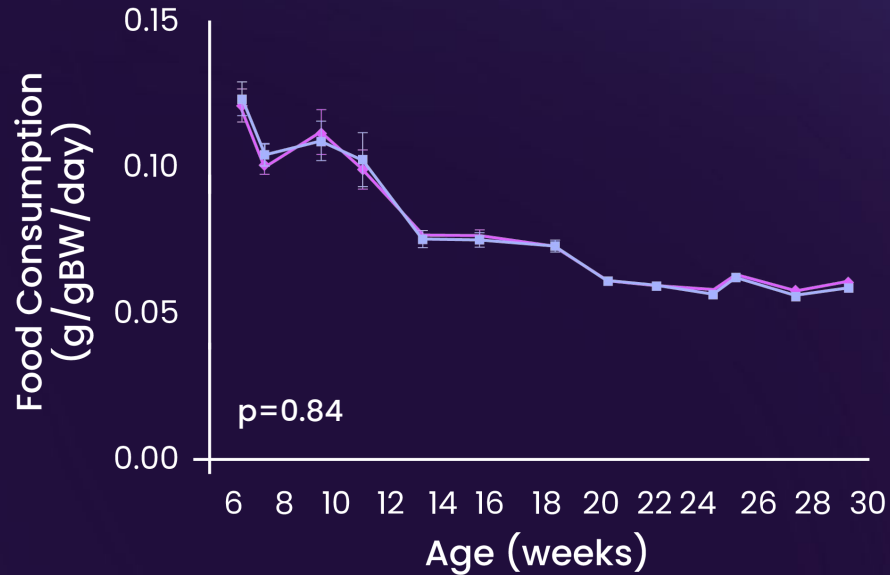
Azelaprag monotherapy on a high-fat diet (27 weeks)





Azelaprag had no significant effect on food intake

Food Intake



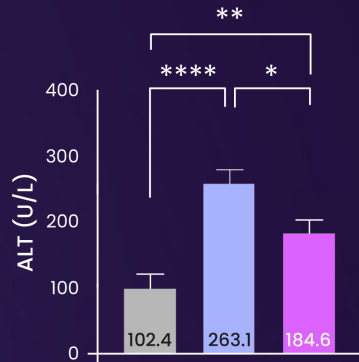
—●— HFD —●— HFD + Azelaprag (3.3 g/L)



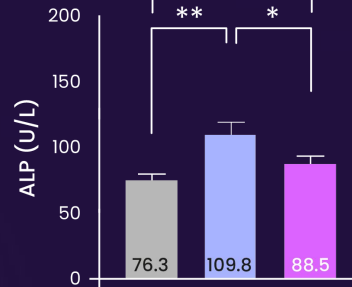
Azelaprag reduced levels of liver enzymes and free fatty acids

Liver enzymes

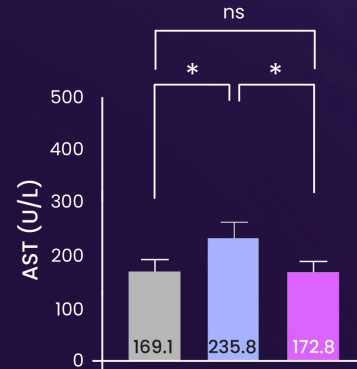
ALT



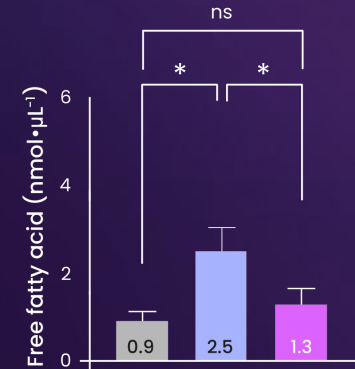
ALP



AST



Free fatty acids



— Lean control

— HFD

— HFD + Azelaprag (3.3 g/L)

Study 2: Azelaprag monotherapy in obese mice



Arms (3 mo tx; n=5-6 per arm)

- Lean control
- Diet-induced obesity
- Diet-induced obesity + azelaprag (1.1 g/L in drinking water)

Metabolic cage measurements

- Energy expenditure (indirect calorimetry)
- X-Y activity

Timeline



1.5 mo

HFD or lean control diet

8.6 mo

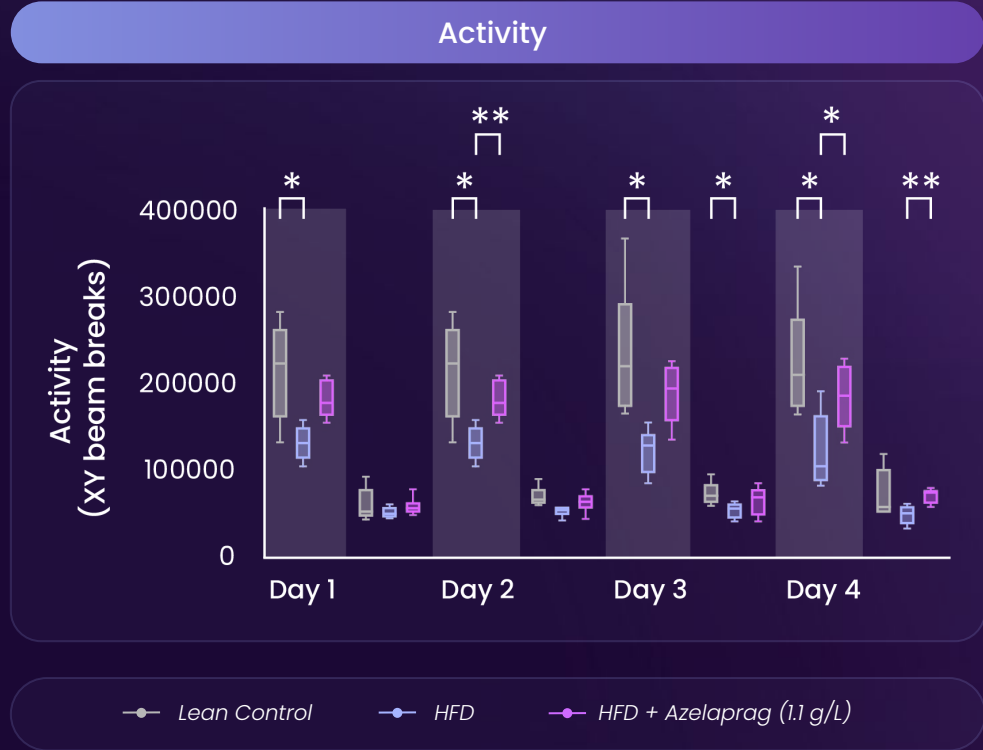
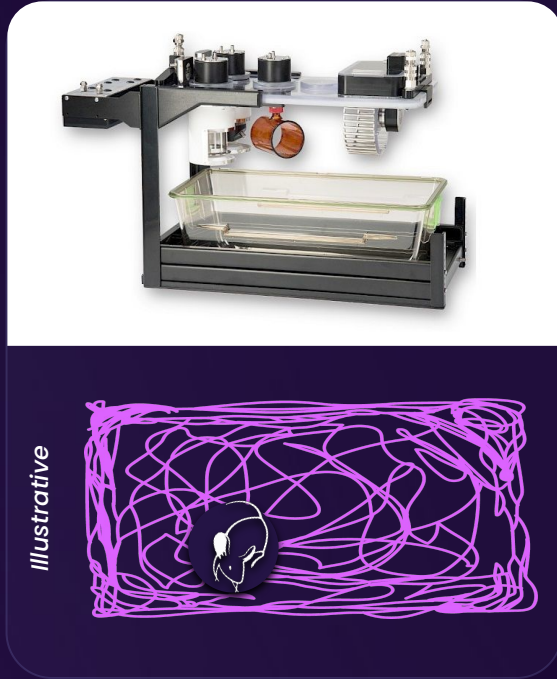
Vehicle or Azelaprag in drinking water

11.7 mo





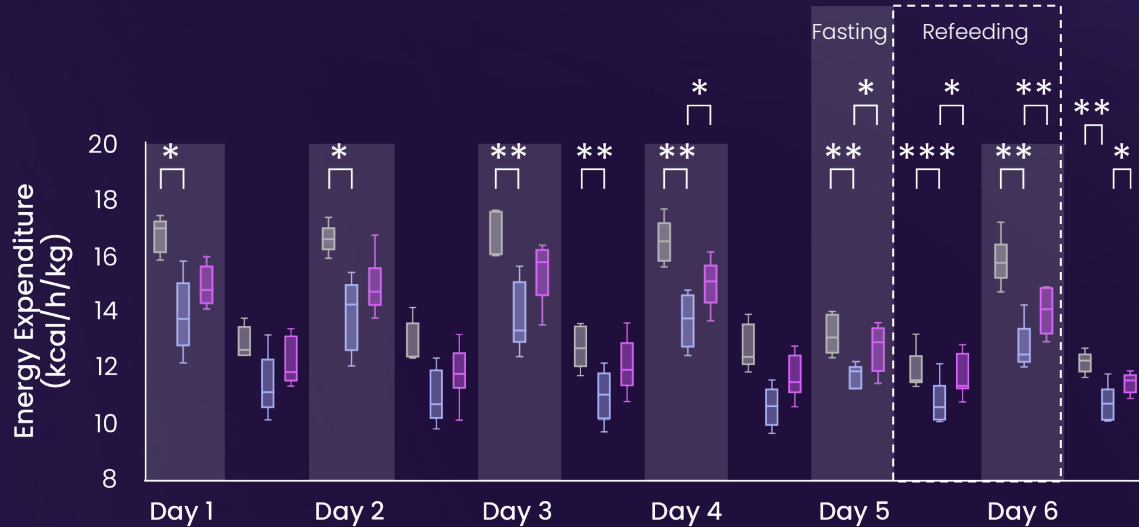
Azelaprag increased activity in obese mice





Azelaprag also increased energy expenditure

Energy expenditure



Our Ph2 STRIDES trial of azelaprag + tirzepatide will focus on older obese patients with 90% power to show approvable weight loss difference

STRIDES Azelaprag + tirzepatide Ph2 trial in obesity

- Adults with obesity**
- Age 55+
 - BMI 30-40
 - Exclude T2D/NASH
 - GLP-1 naive



Primary endpoint
% change in overall weight loss

- Exploratory endpoints**
- Metabolic parameters (e.g., fasting glucose, HbA1c)
 - PROs & QoL
 - Body composition (DEXA)
 - Biomarkers
 - Wearables (activity, sleep)



Power: ~90% power to detect a 3.3% improvement in weight loss over TZP monotherapy. Corresponds to >5% overall weight loss at 1 year.

Summary



Azelaprag could address key unmet needs in obesity treatment: oral efficacy, tolerability, and body composition



The combination of azelaprag and an incretin drug restores body weight, body composition and muscle function to lean control levels without impacting food intake



In a mouse model of diet-induced obesity, azelaprag monotherapy reduced weight gain and improved body composition without impacting food intake



In a separate study, azelaprag increased physical activity and energy expenditure in obese mice



BioAge has initiated the Phase 2 STRIDES trial to evaluate azelaprag in combination with tirzepatide in older adults with obesity

Acknowledgments

Yan Wang

Rusty Montgomery

Robert Hughes

Chris Patil

Ling Chen

Jessica Hussell

Sanjeev Kothari

Ann Neale

Patrick Martin

Samantha Cowdin

Matt Banicki

Joshua VanWinkle

Claudia Portillo

Mary Cochran

Shijun Yan

Gabriel Guerrero