The Apelin Receptor Agonist Azelaprag Increases Weight Loss in Diet-Induced Obese Mice on Incretin Agonists and Restores Body Composition and Muscle Function to that of Lean Controls

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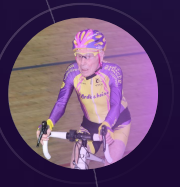
American Diabetes Association 84th Scientific Sessions
June 21, 2024

We are harnessing the biology of human aging to develop new therapies for metabolic diseases



Azelaprag: an oral exercise mimetic for obesity entering Ph2
Potential for best-in-class oral weight loss in combination with an incretin

- Potential first- and best-in-class apelin receptor APJ agonist
- **Core value proposition:** potential 20%+ weight loss in an all-oral incretin combination
- **Potential for significant upside:** improved body composition and tolerability
- **Clinical results:** Muscle and metabolic benefits in Ph1b; well tolerated in >240 subjects
- **Preclinical results:** 2x overall weight loss with incretins in preclinical studies
- **Development plans:** Two Ph2 trials - with Zepbound and Wegovy

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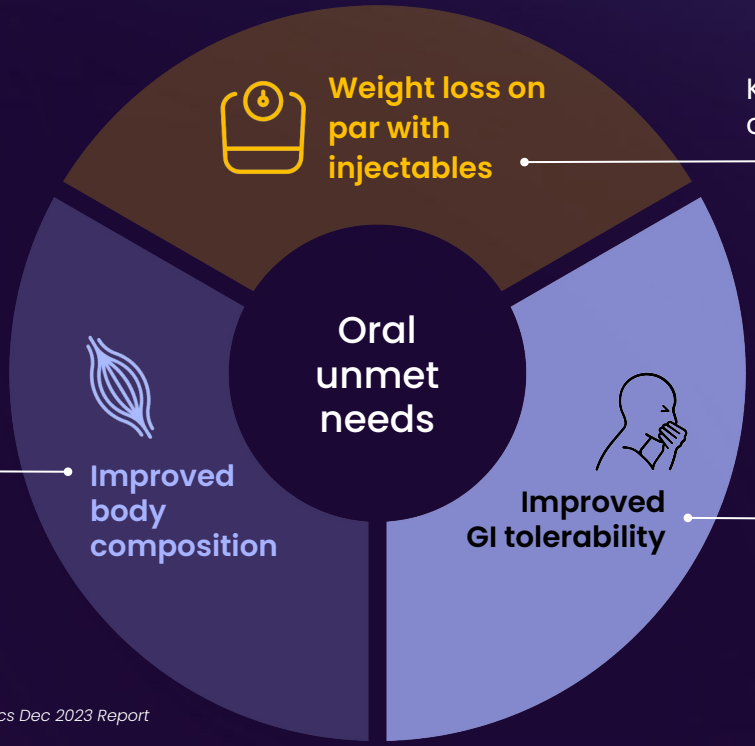
Azelaprag, in combination with an incretin, has the potential to address key unmet needs in obesity: oral weight loss, tolerability, and body composition



Key unmet need & clear regulatory path

Suboptimal body composition is linked to functional deficits & weight regain

58* to 87%** experience GI side effects in Ph2-3 trials of oral incretins

*Source: *Wharton 2023, **Structure Therapeutics Dec 2023 Report*

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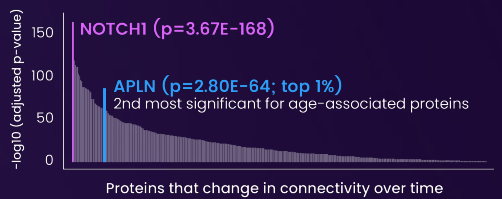
The BioAge platform: Apelin signaling impacts muscle & metabolism

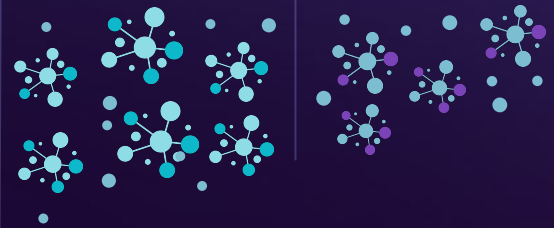
Target ID

Apelin signaling is highly dysregulated with aging

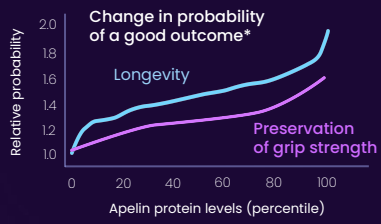
Apelin abundance predicted both function & longevity in our human aging cohorts, and is associated with several metabolic traits

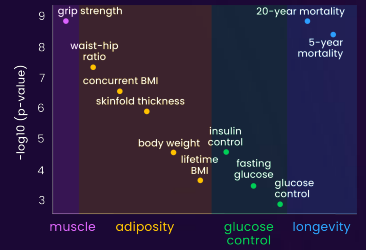


Target validation



Apelin receptor APJ agonist azelaprag demonstrated a range of muscle, functional, and metabolic benefits in mice





Discovery & development

We licensed azelaprag from AMGEN

In a Ph1b trial in healthy elderly volunteers on bed rest, azelaprag prevented muscle atrophy & promoted metabolism with a clean tolerability profile

Improvements shown in:

- Muscle dimensions
- Metabolism
- Muscle quality

*Note: * Shown are smoothed spline fits for apelin protein percentile in a logistic regression model for two separate phenotypes: longevity (living to ≥90 yrs) and preservation of grip strength (living to ≥90 without grip strength decline from baseline of ≥10 kg).*

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

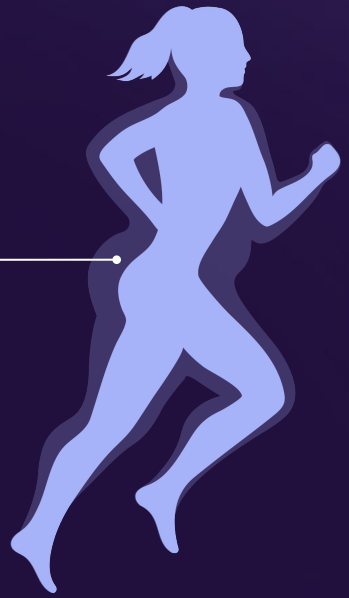
Exercise mimetics for obesity

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

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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

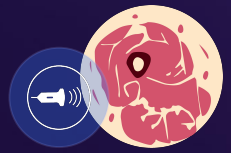
Muscle size

Thigh circumference

Muscle size (Vastus lateralis)

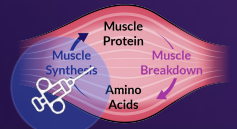
Fat infiltration

Muscle degeneration



Metabolism

Muscle protein synthetic rate



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

Serum proteomics

Single-nucleus transcriptomics

- Resting energy expenditure
- Cardiorespiratory fitness: VO_2 max
- ↑ Oxidative metabolism
  ↑ Glucose control
- ↑ Lipid metabolism

*Note: * 5 /10 (50%) of subjects on placebo and 8/11 (73%) on Azelaprag reported treatment-emergent adverse events; all were mild; most common were headache and procedural (biopsy) pain*

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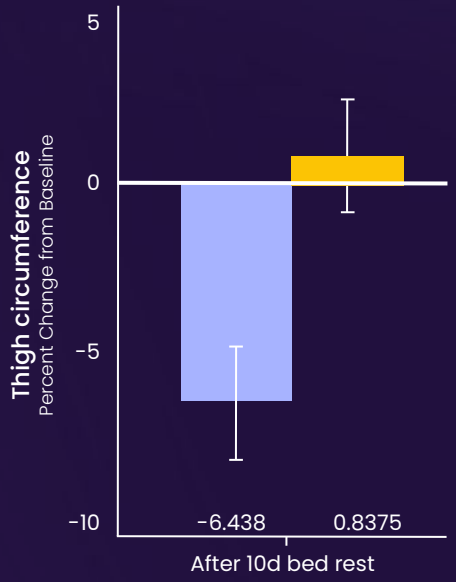
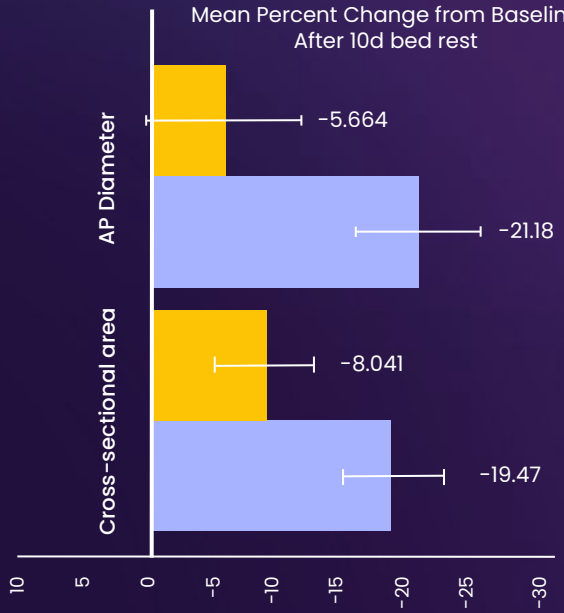
Muscle size

Azelaprag reduced the impact of bed rest on both thigh circumference (p<0.001) and muscle thickness (p<0.01) & cross-sectional area (p<0.05)

Thigh circumference



Vastus lateralis ultrasound



Treatment Group — Placebo — Azelaprag

Note: measurements made 15 cm superior of the mid patella

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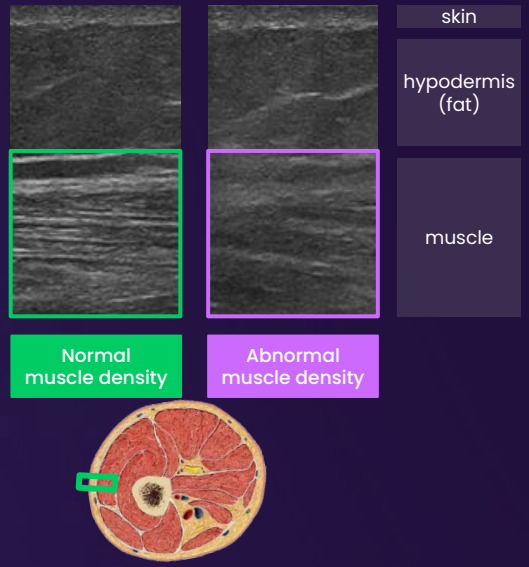
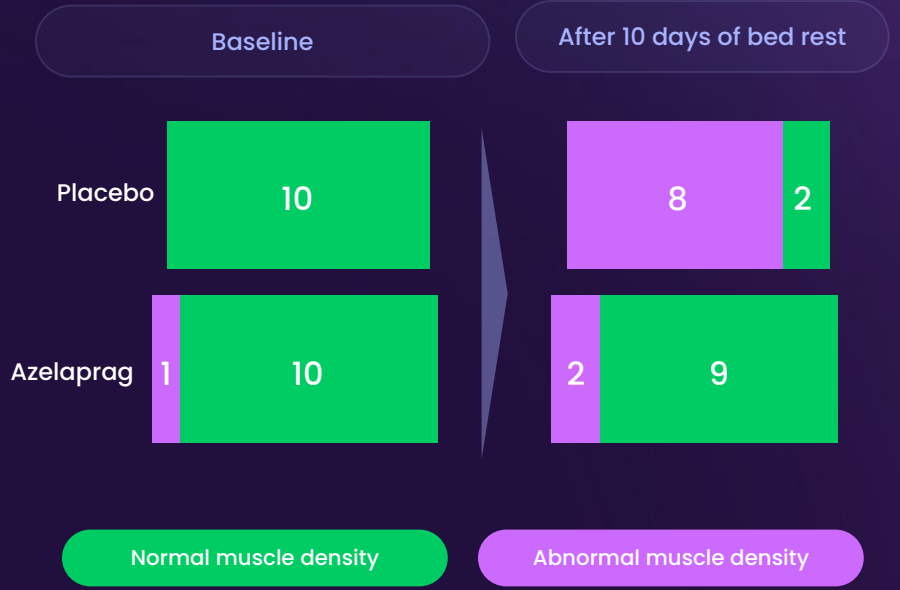
Fat infiltration

Azelaprag mitigated bed rest-induced muscle quality degradation via echo density (p<0.005)

Fat infiltration: Azelaprag significantly reduced muscle quality degradation on bed rest

Representative ultrasound images of normal and abnormal muscle





8/10 placebo subjects show decreased muscle quality

vs **1/11** for azelaprag subjects

Note: The same result was observed in the vastus lateralis and gastrocnemius muscles
Source: McGregor 2014

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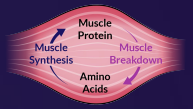
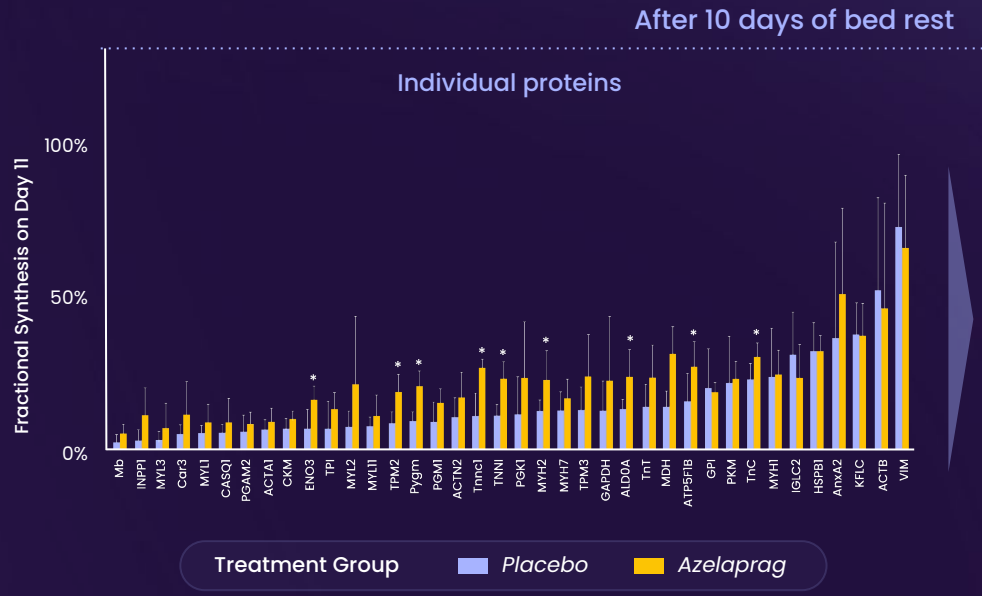
AZELAPRAG: PH1B RESULTS

Azelaprag resulted in relatively higher muscle protein synthesis in vastus lateralis microbiopsies (p<0.005)

Vastus lateralis microbiopsy





Note: p value based on a t-test comparing per-patient normalized FSR values across all common proteins (N=38)

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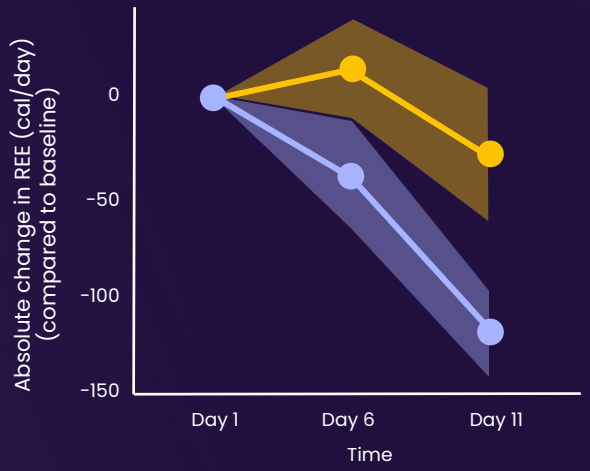
Azelaprag-induced shifts in the serum proteome that are indicative of preserved resting energy expenditure and VO_2 max

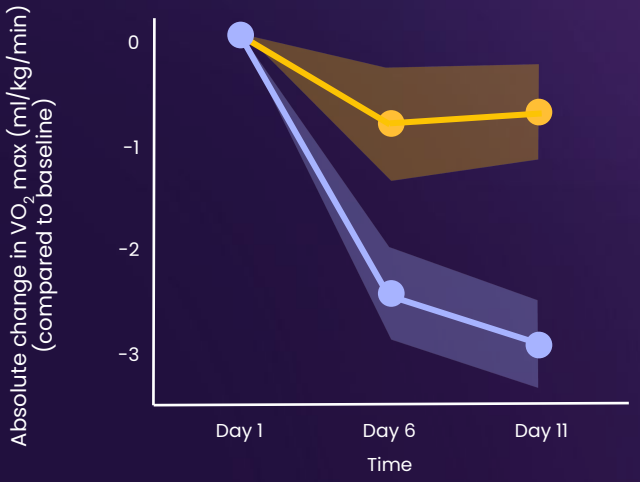
Predicted resting energy expenditure

End of treatment: p=0.03



Predicted cardiorespiratory fitness: VO_2 max

End of treatment: p=0.004



Treatment Group — *Placebo* — *Azelaprag*

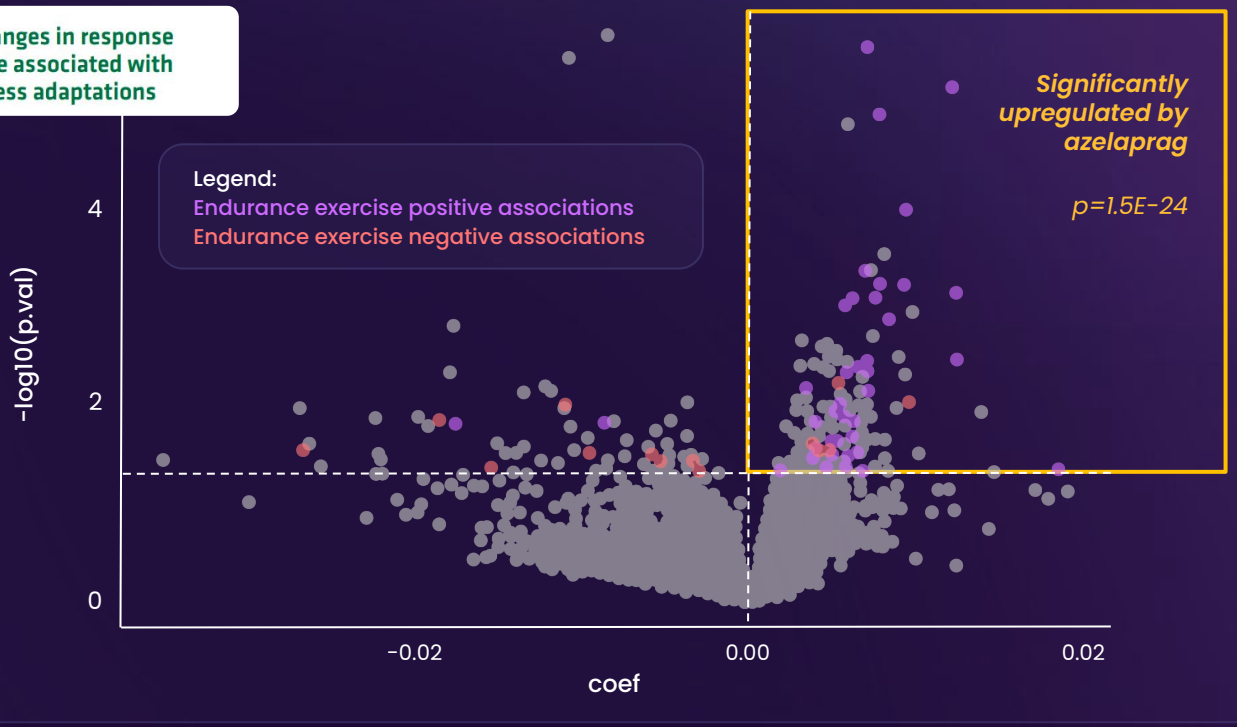
Note: SomaSignal tests scan for proteomic markers across dozens of disease areas, allowing the accurate identification of patients who are at highest risk of a health event, for research use only (https://somalogic.com/somasignal-tests/).

AZELAPRAG: PH1B RESULTS

Azelaprag shifted the serum proteome consistent with being an exercise mimetic

JCI insight

Plasma proteomic changes in response to exercise training are associated with cardiorespiratory fitness adaptations



Source: Robbins 2023

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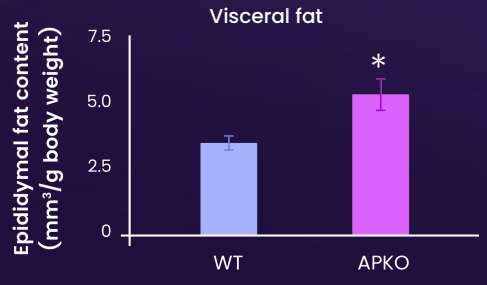
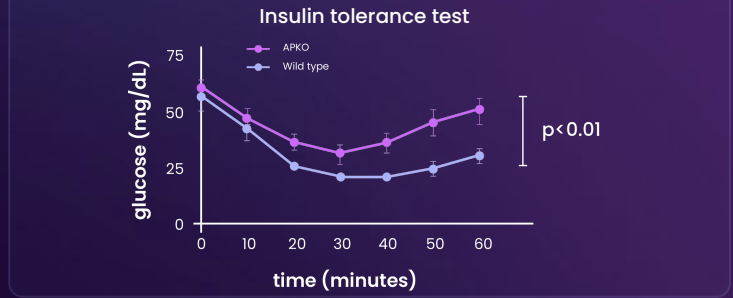
Apelin genetics reinforce beneficial role in systemic metabolism

Apelin KO

↑ adiposity

↑ insulin resistance



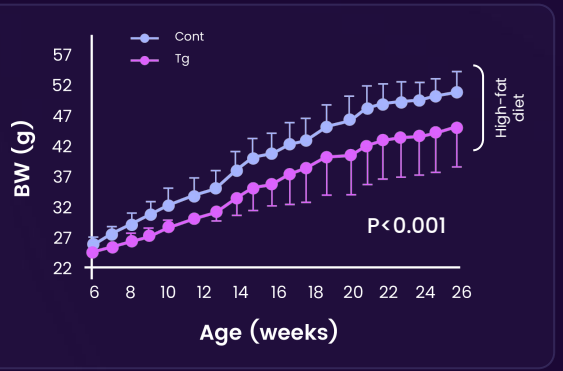


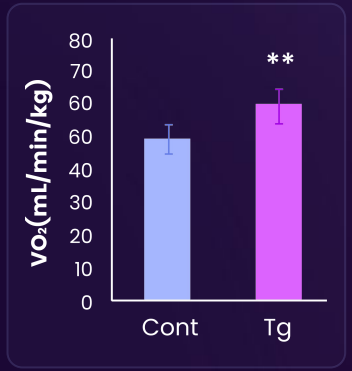
Apelin transgenic

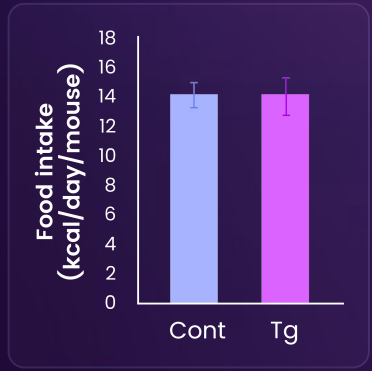
↓ weight gain on high fat diet

↑ 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

Source: Yue 2010; Yue 2011; Yamamoto 2011; Pulit 2019; Sakaue 2021; Pei 2020; Richardson 2020; Wakil 2016

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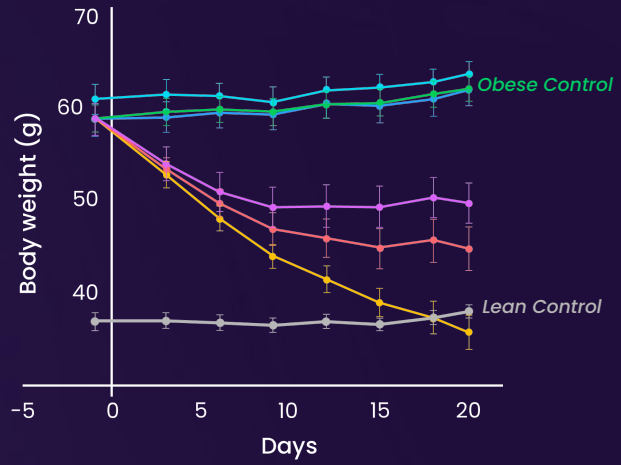
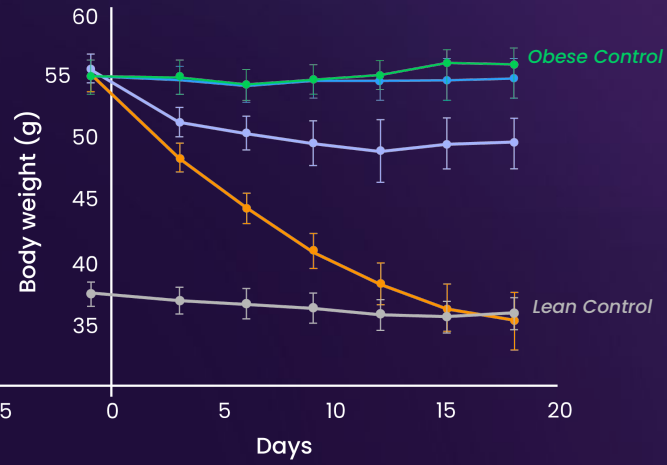
Azelaprag increased overall weight loss with tirzepatide to ~40%; similar results observed with semaglutide suggest a class effect

Overall weight loss

Tirzepatide



Semaglutide



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

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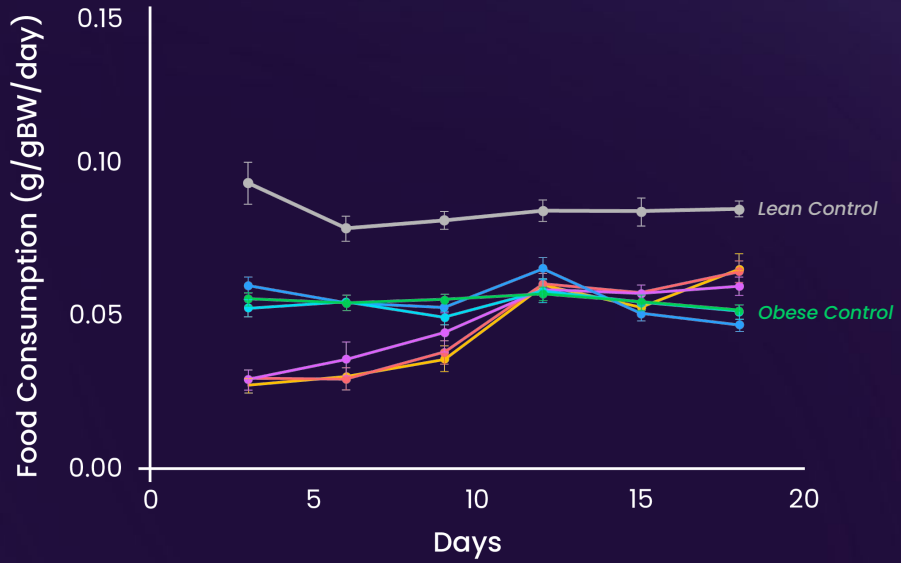
Azelaprag increased overall weight loss without material impacts on energy intake

Daily food consumption (g/gBW/day)



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

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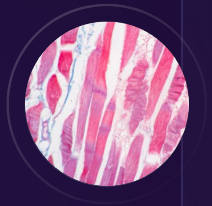
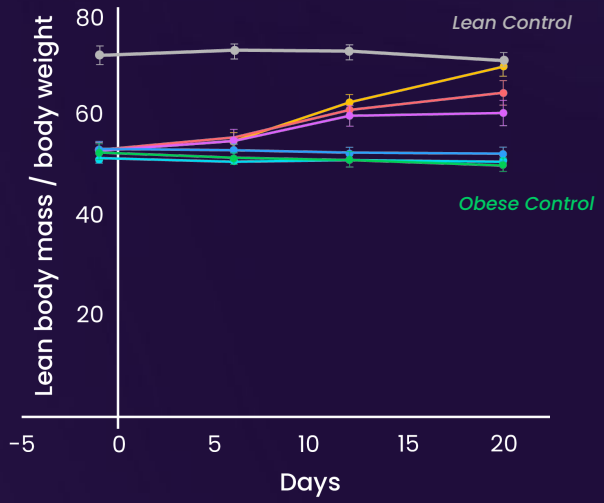
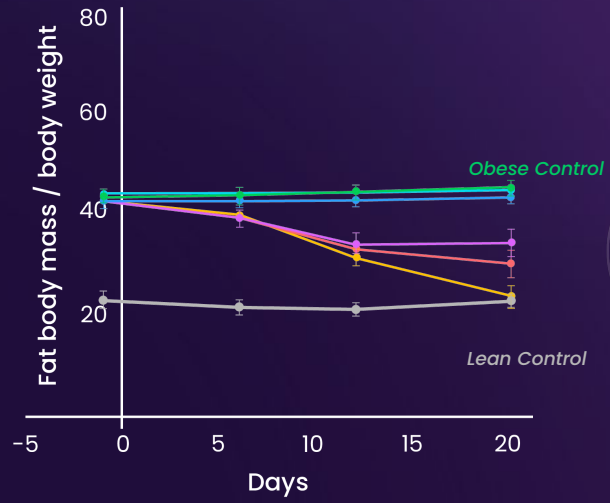
Addition of azelaprag to tirzepatide restored body composition to that of lean controls in a dose-dependent fashion

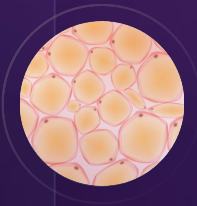


% Lean Mass by EchoMRI



% Fat Mass by EchoMRI



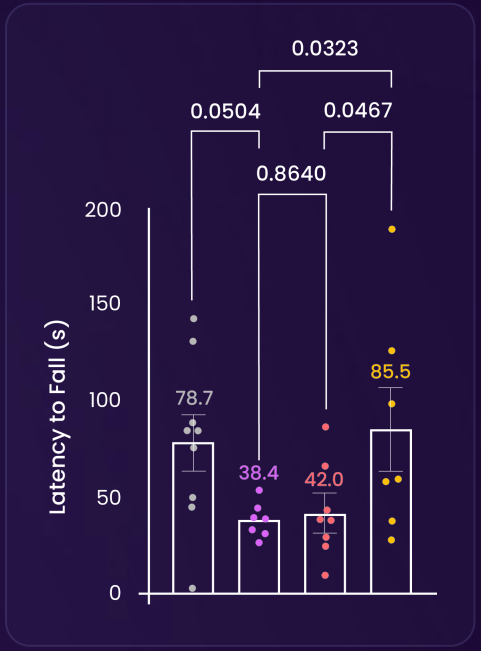


Lean Control
Vehicle
Azelaprag (0.275g/L)
Azelaprag (1.1g/L)
Tirzepatide (10nmol/kg)
Tirzepatide (10nmol/kg)+ Azelaprag (0.275g/L)
Tirzepatide (10nmol/kg)+ Azelaprag (1.1g/L)

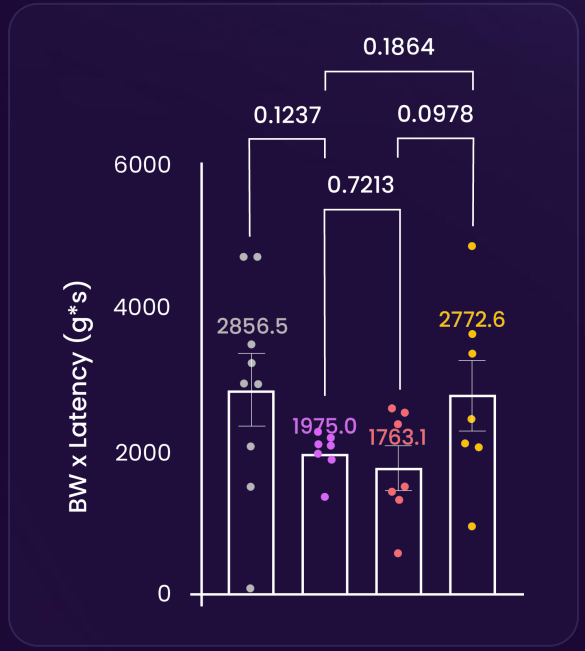
Note: Mice in all groups lose both lean mass and fat mass; with Azelaprag, lean body composition (% lean mass) is restored

Azelaprag improved body composition and fully restored muscle function to that of lean controls *(N=7 per group)*

Grid Hang Tests-Latency



Grid Hang Tests-BW x Latency



- *Lean Control (N=9)*
- *Tirzepatide (10nmol/kg) (N=7)*
- *Tirzepatide (10nmol/kg)+ Azelaprag (0.275g/L) (N=7)*
- *Tirzepatide (10nmol/kg)+ Azelaprag (1.1g/L) (N=7)*

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

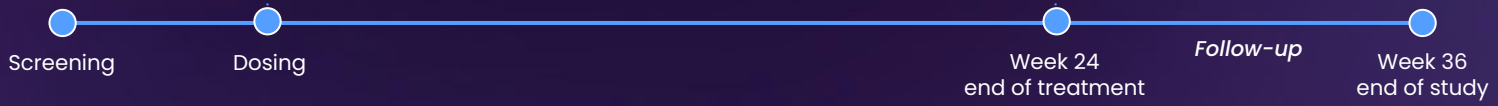
STRIDES Azelaprag + tirzepatide Ph2 trial in obesity

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

TZP 5mg SC QWK	Placebo PO QD	N=66
TZP 5mg	Azelaprag 300 mg QD	N=66
TZP 5mg	Azelaprag 300 mg BID	N=66
Placebo	Azelaprag 300 mg BID	N=22

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
- In a preclinical model of diet-induced obesity, the combination of Azelaprag and an incretin drug restored body weight, body composition and muscle function to levels of lean controls, without impacting food intake
- Azelaprag mimics the effects of exercise in humans: In Phase 1b trial, prevented muscle loss and increased energy expenditure in older adults on bed rest
- BioAge plans to initiate the Phase 2 STRIDES trial in mid-2024 to evaluate azelaprag in combination with tirzepatide in older adults with obesity

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