

# Murine bimagrumab co-administration with incretin agonists results in additive efficacy and superior quality weight loss in the mouse diet-induced obesity model

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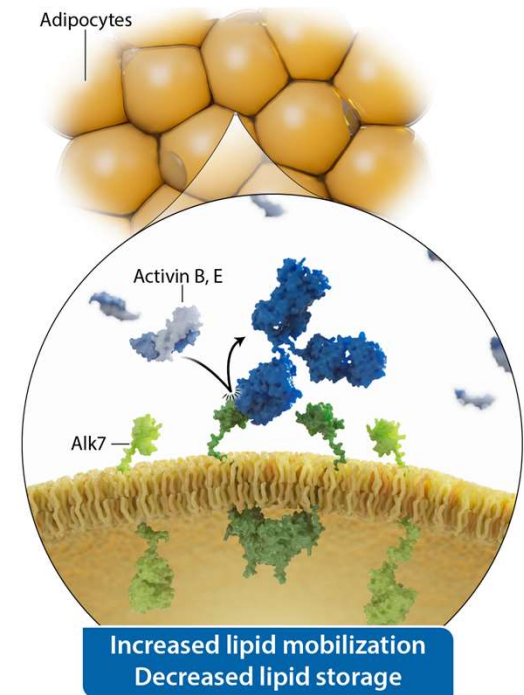
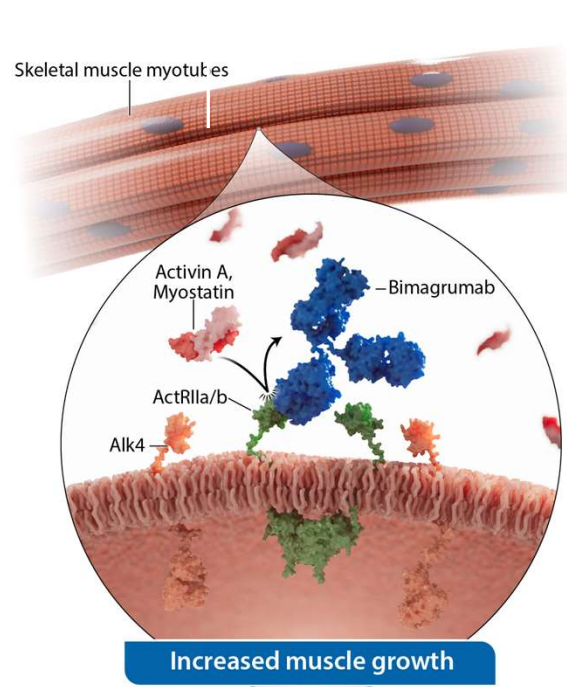
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# Introduction to bimagrumab:

*Blocking antibody to activin type II receptors increases muscle mass and decreases fat mass*

- Bimagrumab is a potent, first-in-class, fully human monoclonal antibody to ActRIIA and ActRIIB that blocks ligand binding in muscle and adipose tissue to increase muscle mass while causing fat loss
- Bimagrumab is a clinical stage drug candidate studied in 22 human trials to date
- The mouse version of bimagrumab is called CDD866

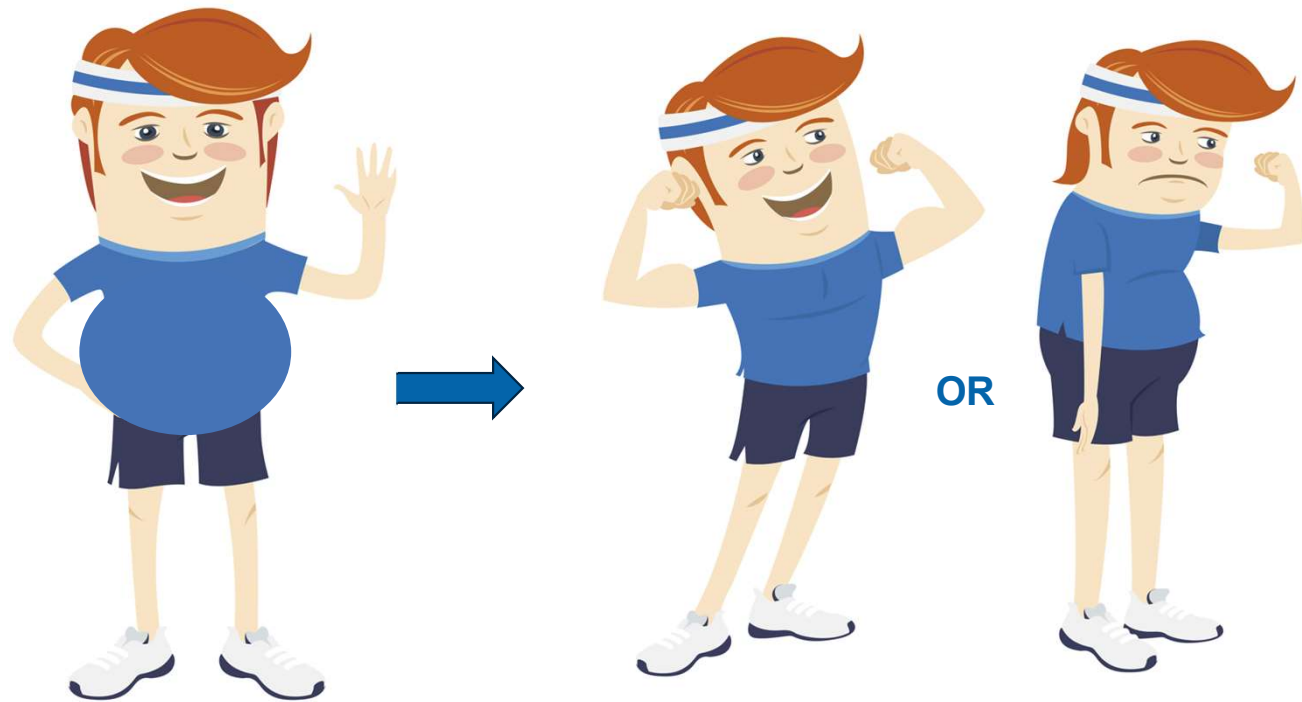


# Introduction to weight loss quality (WLQ):

*The % of body weight loss attributable to fat mass loss*

**Quality matters; losing muscle mass during treatment for obesity doesn't help patients**

$$\text{WLQ} = \frac{\text{Fat mass loss}}{\text{Total weight loss}} \times 100$$



## In humans, bimagrumab weight loss quality is superior to that of incretins

	Semaglutide 68 weeks	Tirzepatide 72 weeks	Bimagrumab 48 weeks
Fat mass	↓ -8.4 kg (-19.3%)	↓ -16.7 kg (-33.9%)	↓ -7.3 kg (-20.0%)
Body weight	↓ -13.6 kg (-11.4%)	↓ -22.4 kg (-22%)	↓ -5.1 kg (-5.7%)
Weight loss quality	↓ 61%	↓ 75%	↑ 143%
Lean mass	↓ -5.2 kg (-9.7%)	↓ -5.7 kg (-10.9%)	↑ +2.1 kg (+4.4%)

What would happen if we were to **combine** bimagrumab with incretins?

Semaglutide and Tirzepatide data are derived from studies in non-diabetic patients; bimagrumab data are from a study in diabetic patients

Semaglutide data derived from STEP 1 study (Wilding JPH et al. NEJM 2021, Wilding JPH et al. J Endocr Soc. 2021 May 3; 5(Suppl 1))

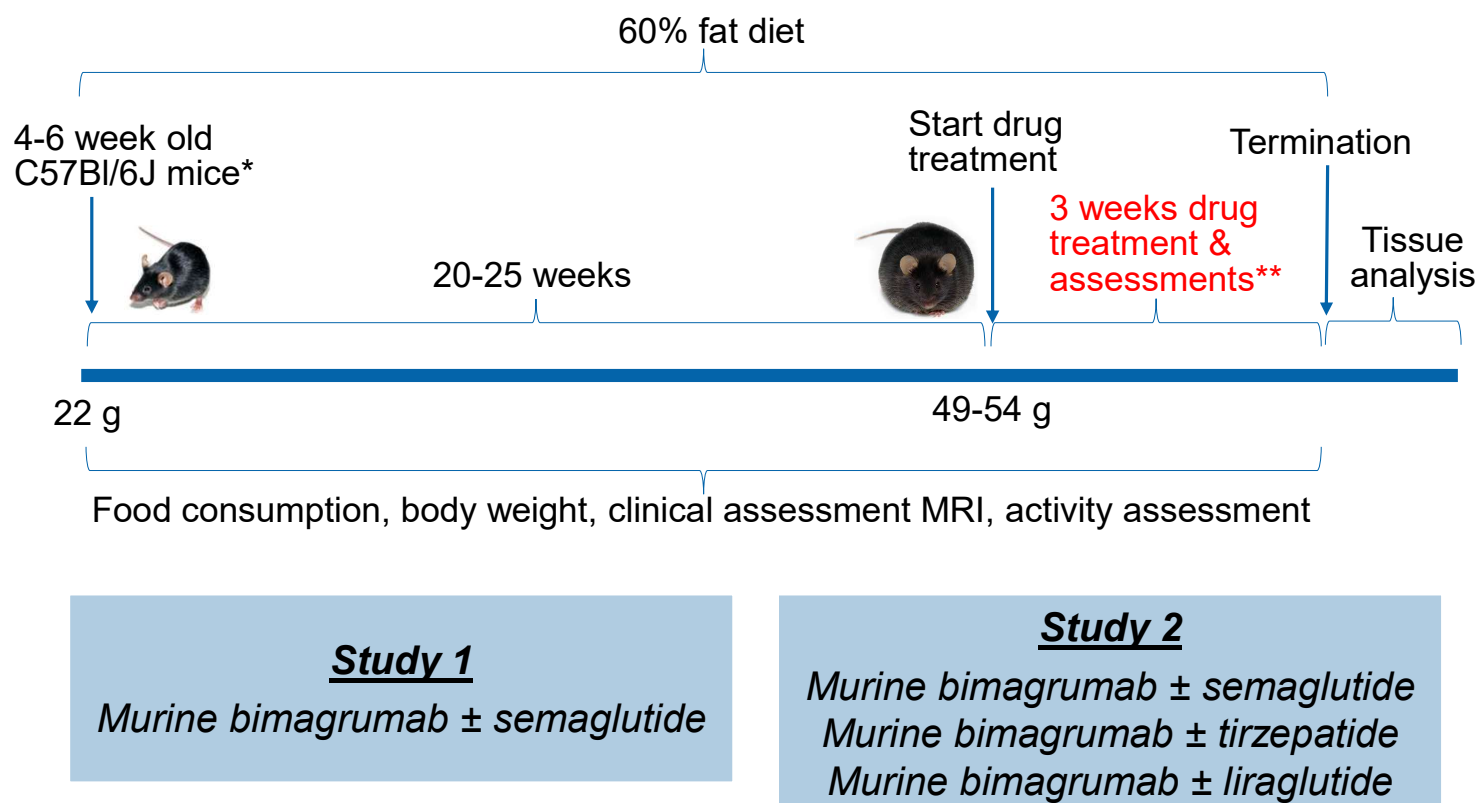
Tirzepatide data derived from SURMOUNT-1 (Jastreboff AM et al, NEJM 2022; 387:205-216, Tirzepatide-Induced Weight Loss Is Associated With Body Composition Improvements Across Age Groups. Robert F. Kushner et al. Obesity Week 2022

Bimagrumab data from Phase 2 study (Heymsfield et al. JAMA Open 2021)

# Study design for murine bimagrumab<sup>‡</sup> + incretin combination pharmacology studies in a diet induced obesity (DIO) mouse model



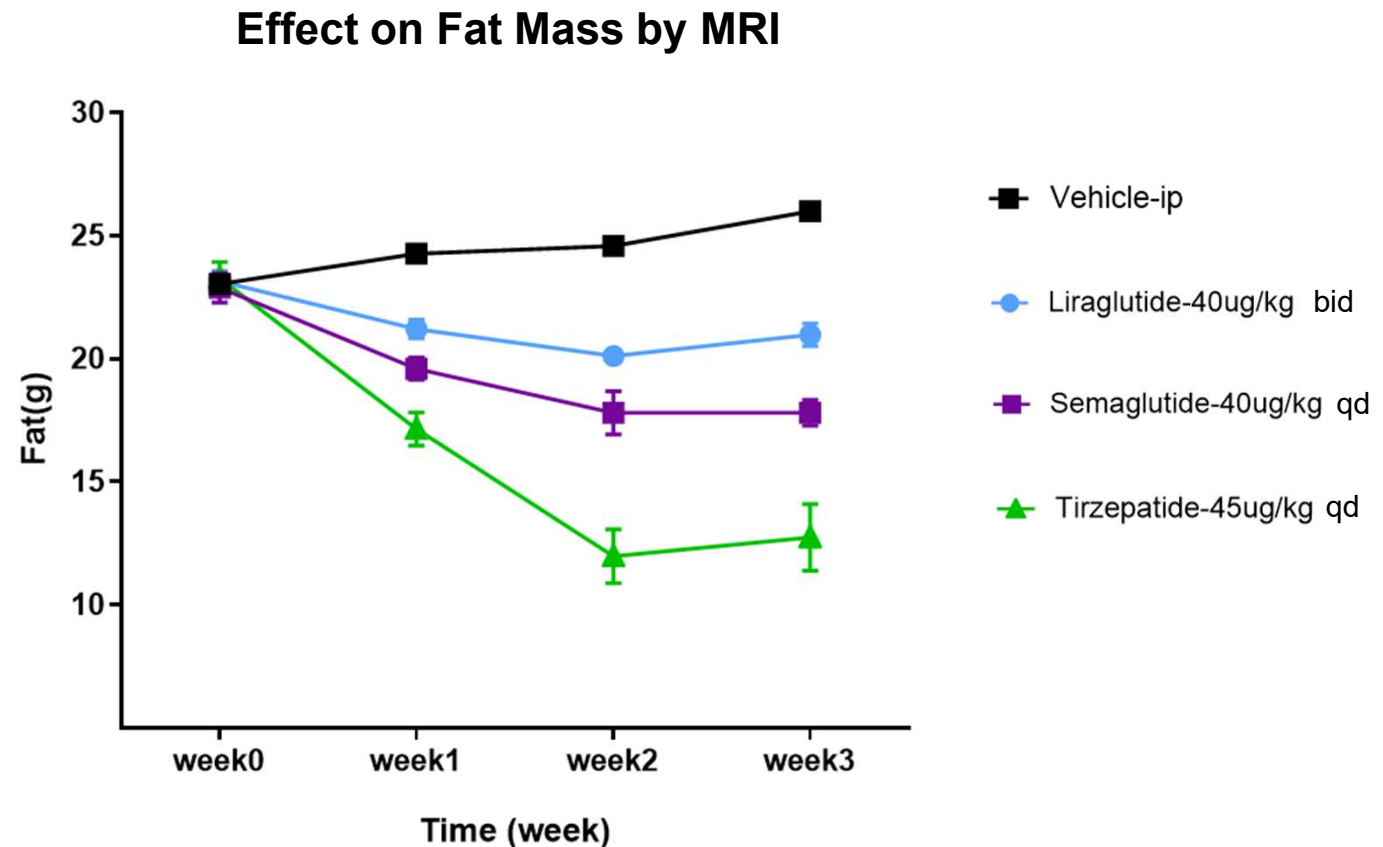
*Bimagrumab is immunogenic in mice:*  
Murine bimagrumab (CD866<sup>‡</sup>) was constructed to decrease immunogenicity and facilitate repeat dose mouse experiments



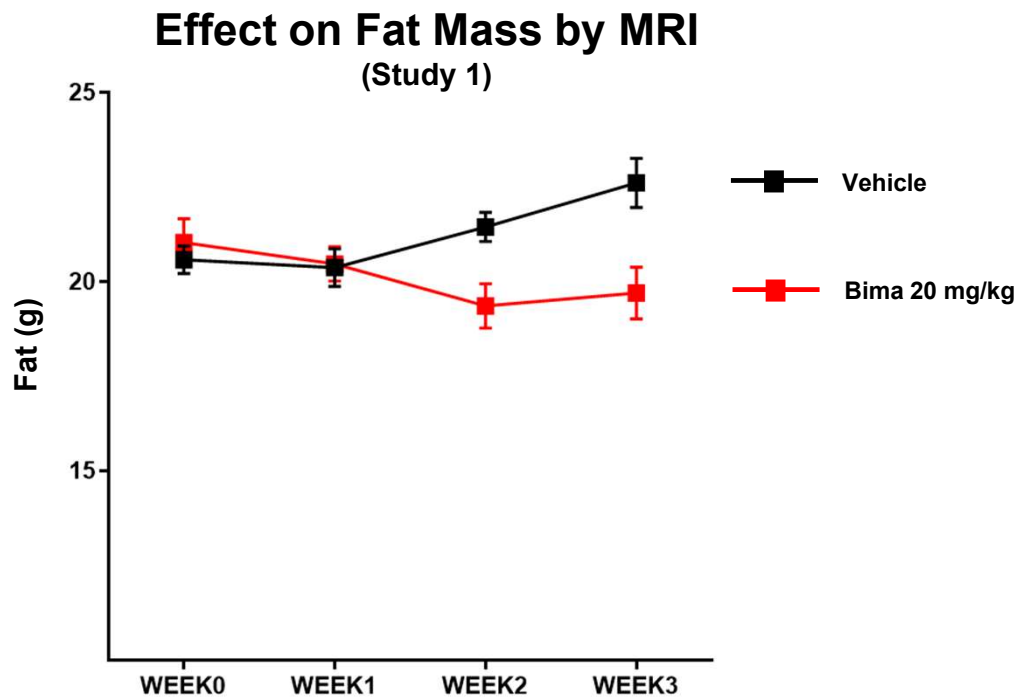
<sup>‡</sup>CD866, a chimeric murine bimagrumab analog is referred to as murine bimagrumab or “bima” throughout this presentation

\*n=8 mice per group; \*\*Assessments included food consumption, body weight, clinical exam, quantitative activity measurement, body composition by MRI, terminal assessments including muscle and fat weights

## The potency of incretin agonists in the DIO model parallels that observed in humans

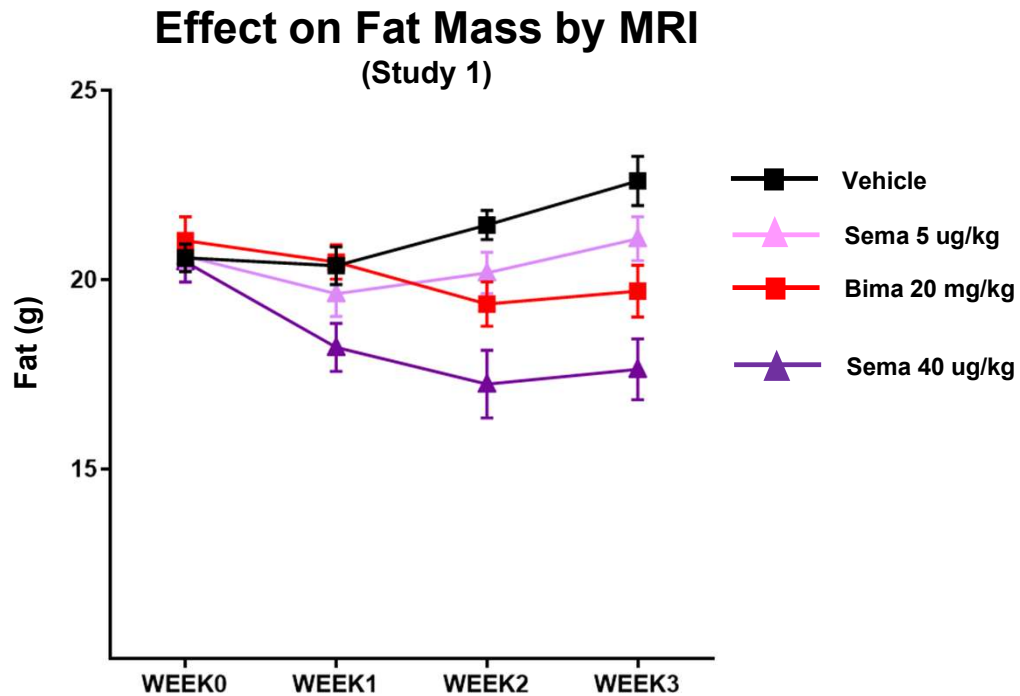


# Effect of murine bimagrumab + incretin treatment on fat mass



Abbreviations: bima – murine bimagrumab; sema – semaglutide; tirze - tirzepatide

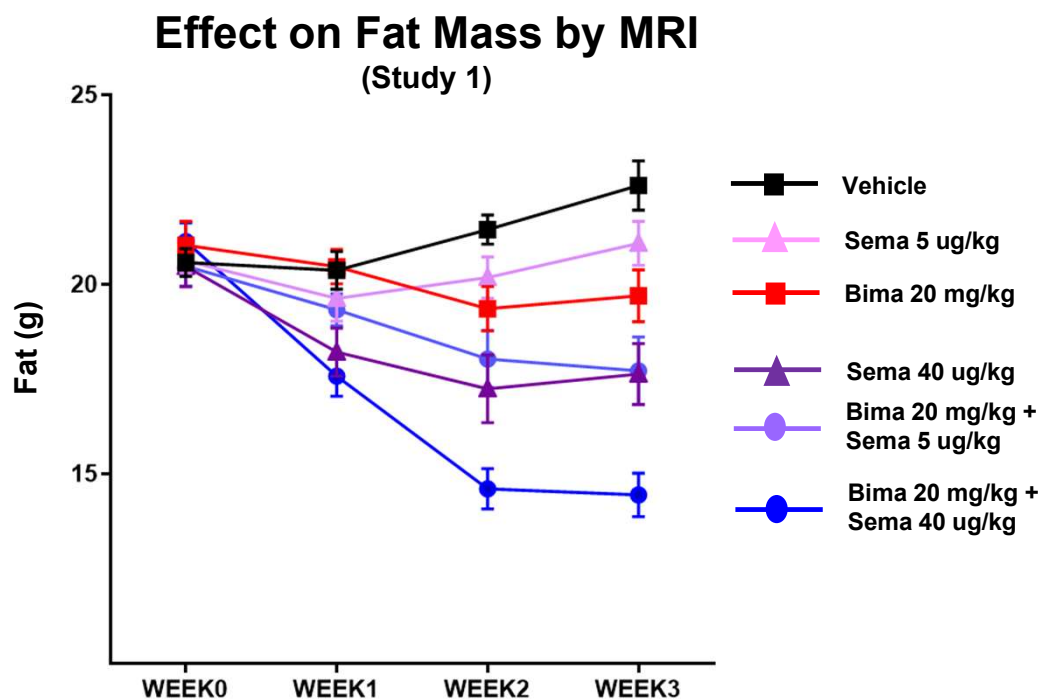
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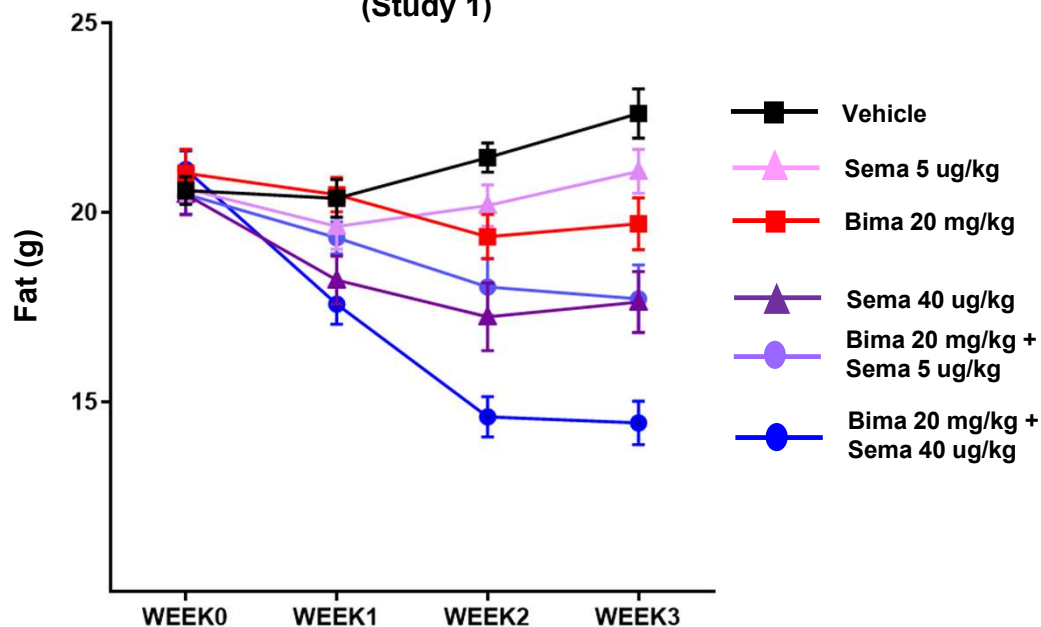
# Effect of murine bimagrumab + incretin treatment on fat mass



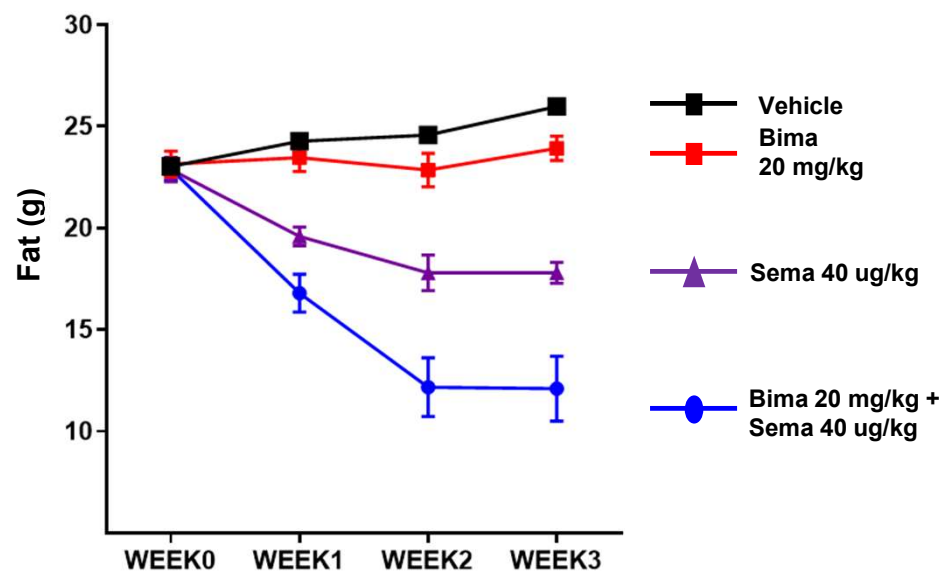
Abbreviations: bima – murine bimagrumab; sema – semaglutide; tirze - tirzepatide

# Effect of murine bimagrumab + incretin treatment on fat mass

**Effect on Fat Mass by MRI**  
(Study 1)



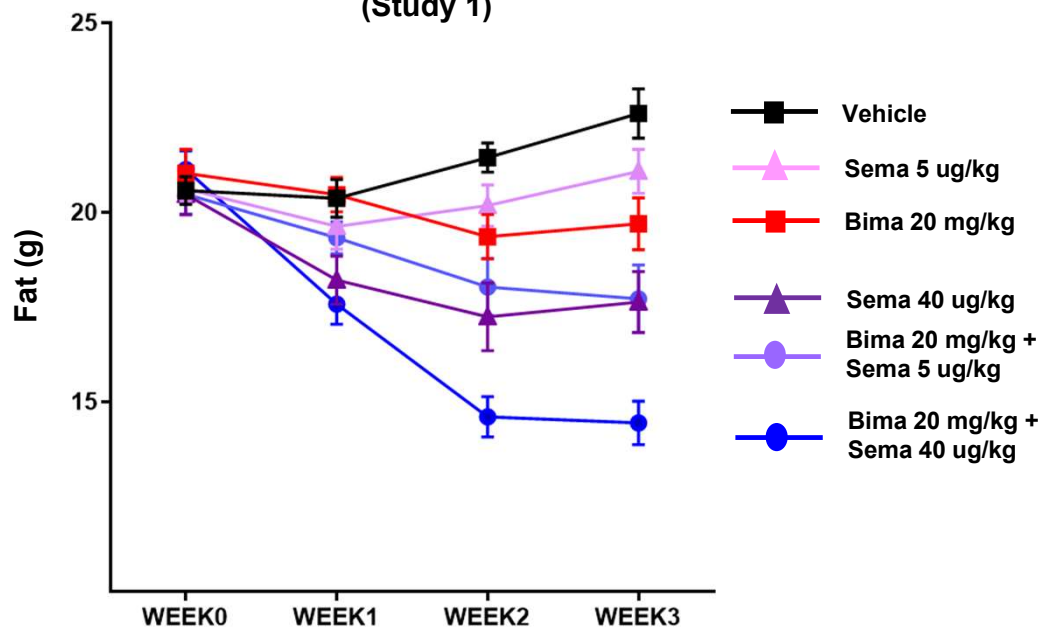
**Effect on Fat Mass by MRI**  
(Study 2)



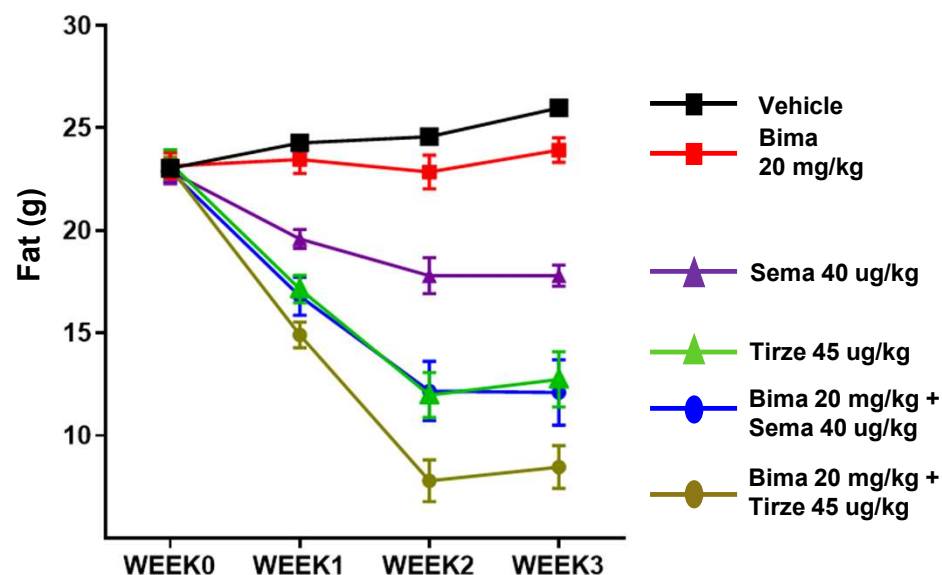
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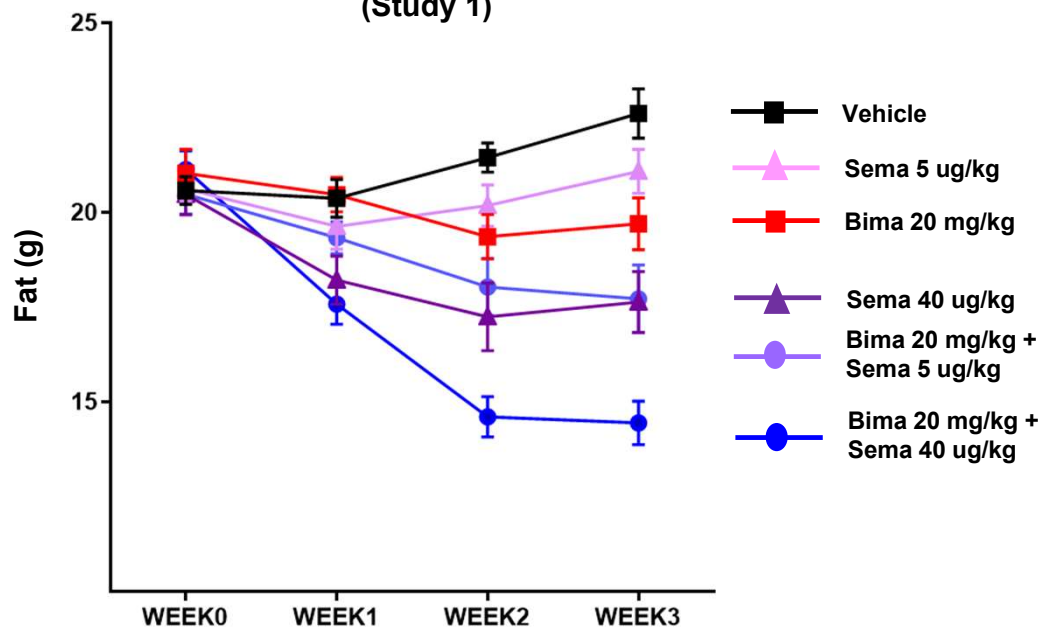
**Effect on Fat Mass by MRI**  
(Study 2)



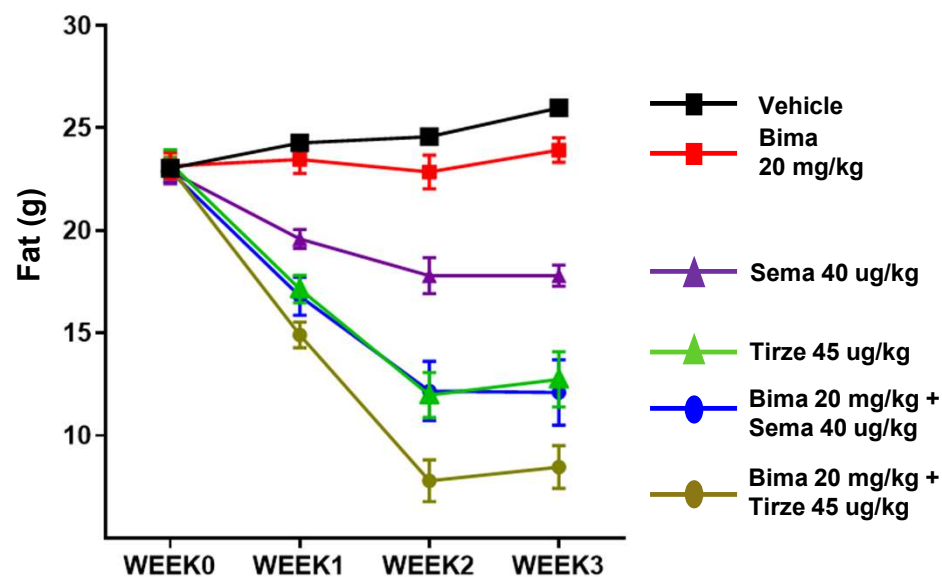
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# Effect of murine bimagrumab + incretin treatment on fat mass

**Effect on Fat Mass by MRI**  
(Study 1)



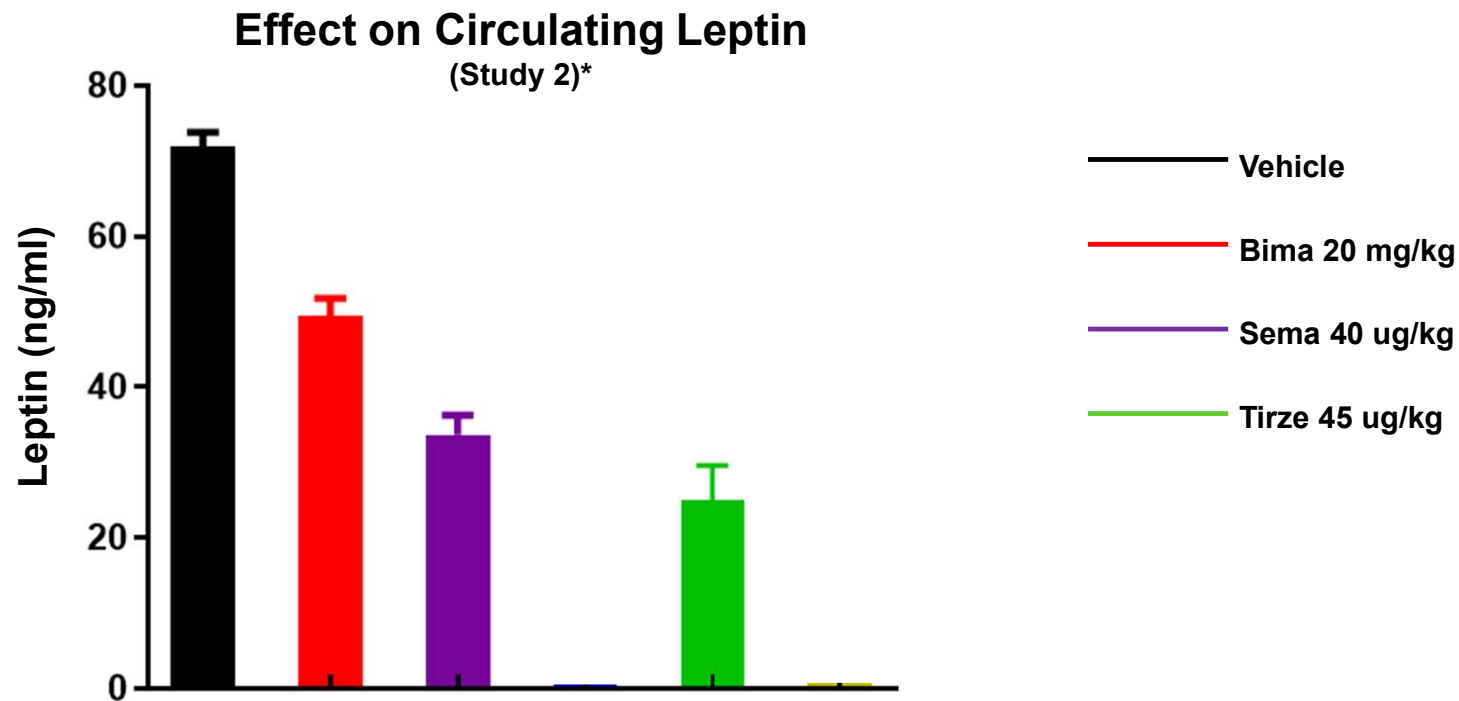
**Effect on Fat Mass by MRI**  
(Study 2)



*Combination of murine bimagrumab with semaglutide or tirzepatide drove additive reduction in fat mass*

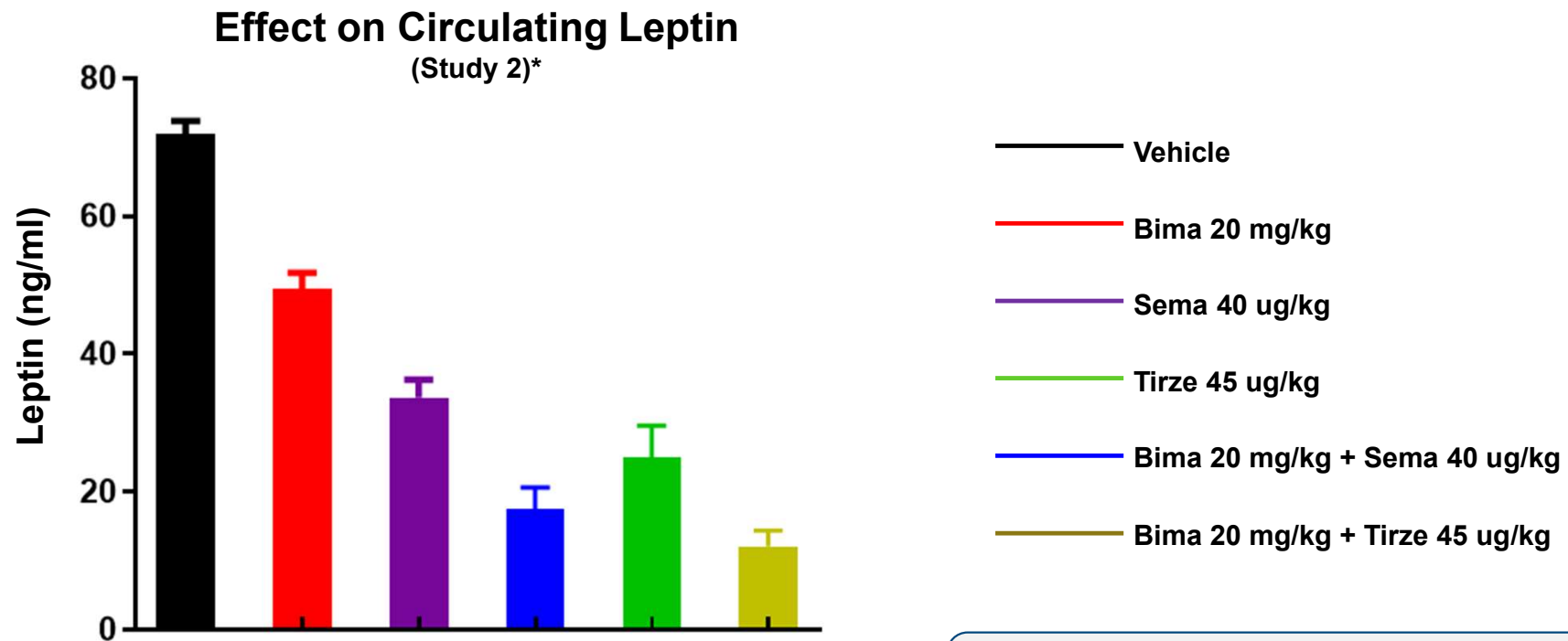
Abbreviations: bima – murine bimagrumab; sema – semaglutide; tirze – tirzepatide.

## Effect of murine bimagrumab + incretin treatment on leptin after 3 weeks of treatment



\*Similar results seen in Study 1 with murine bimagrumab and semaglutide

## Effect of murine bimagrumab + incretin treatment on leptin after 3 weeks of treatment



*Combination of murine bimagrumab + semaglutide or tirzepatide reduced circulating leptin levels by ~80%*

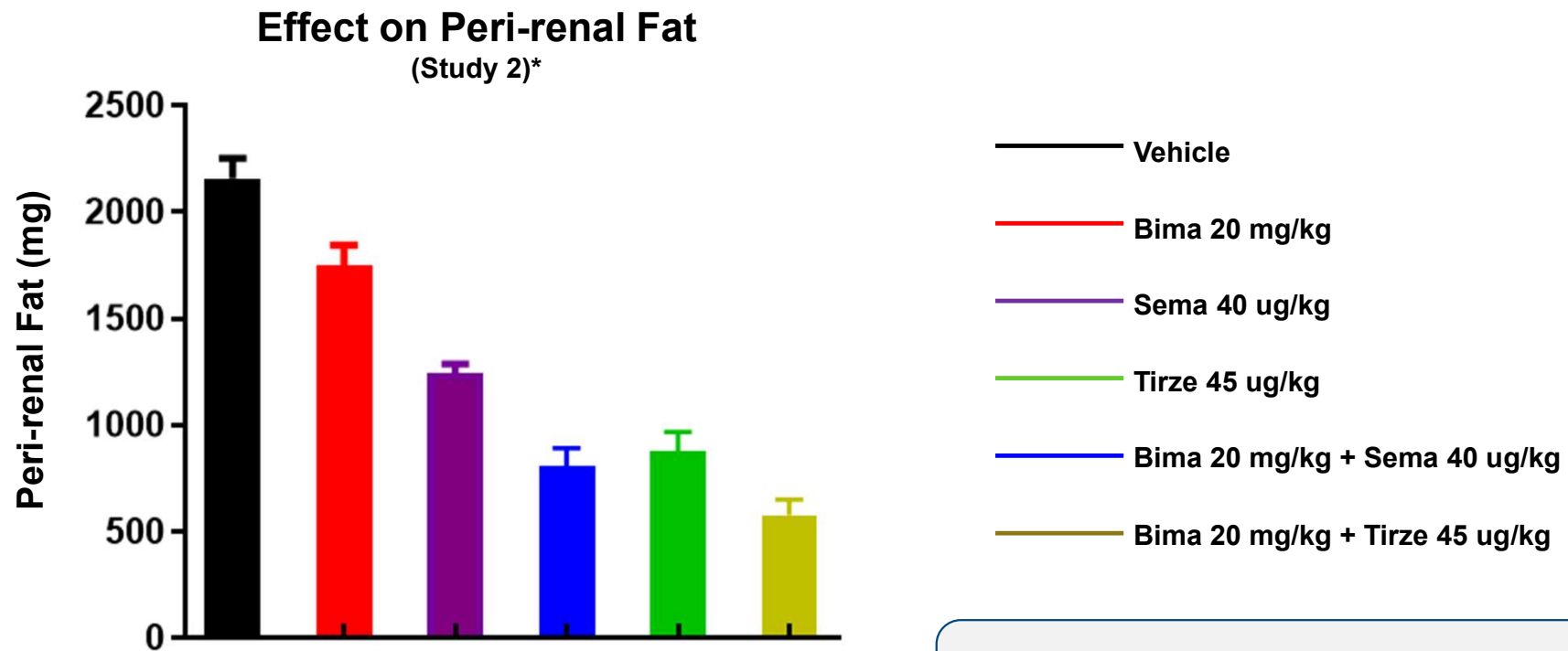
\*Similar results seen in study 1 with murine bimagrumab and semaglutide

## Effect of murine bimagrumab + incretin treatment on peri-renal fat after 3 weeks of treatment



\*Similar results seen in study 1 with murine bimagrumab and semaglutide on inguinal fat

## Effect of murine bimagrumab + incretin treatment on peri-renal fat after 3 weeks of treatment

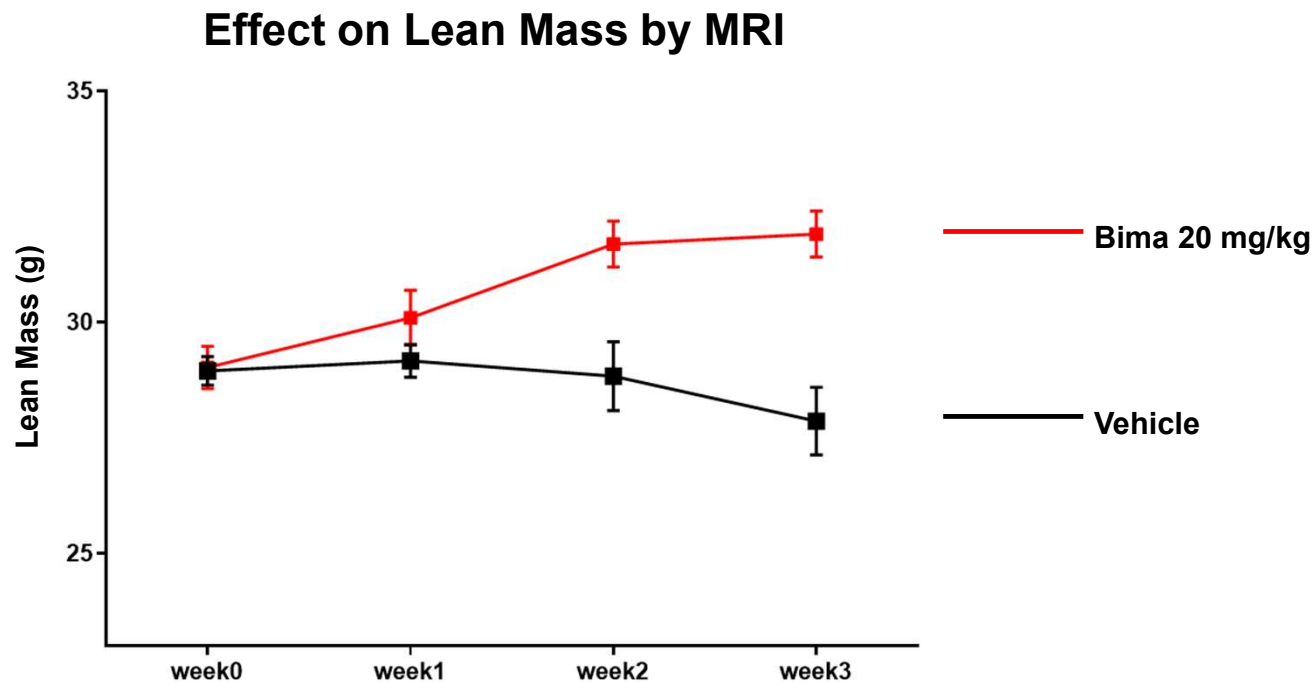


*Combination of murine bimagrumab + semaglutide or tirzepatide reduced peri-renal fat by ~60%*

\*Similar results seen in study 1 with murine bimagrumab and semaglutide on inguinal fat

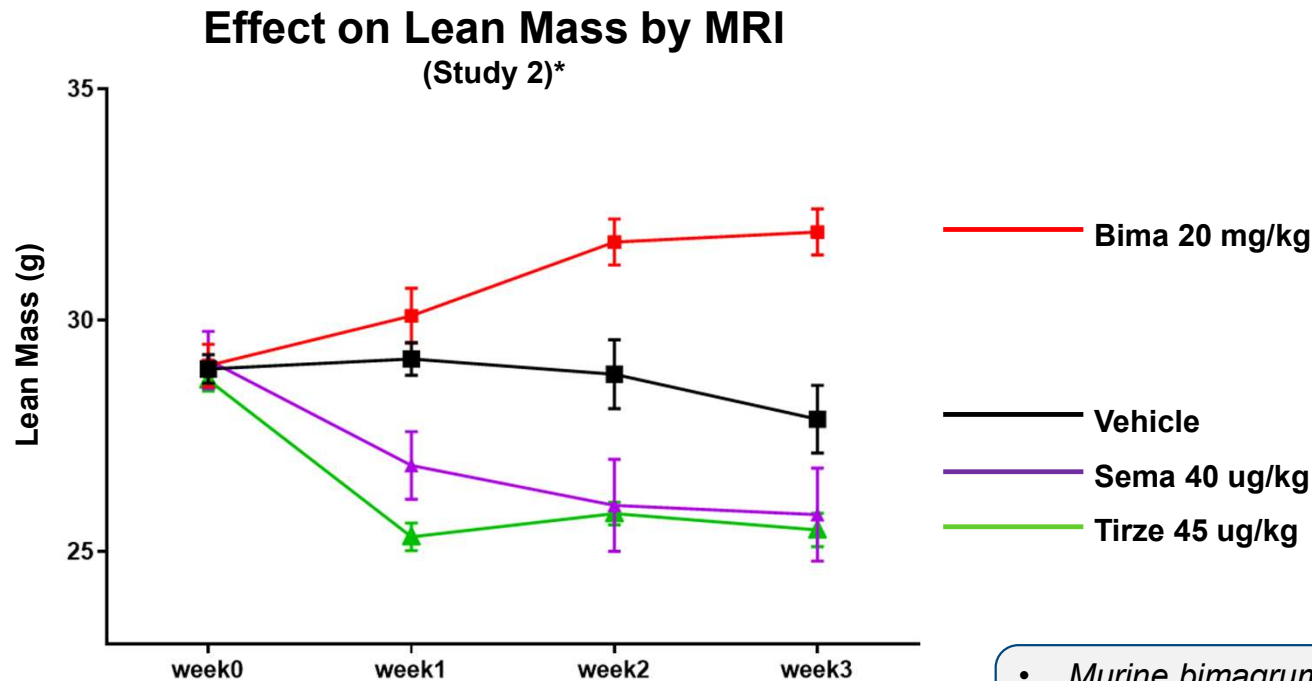


## Effect of murine bimagrumab + incretin treatment on lean mass



*\*Similar results seen in both studies with murine bimagrumab and semaglutide on terminal measurement of gastrocnemius muscle weight*

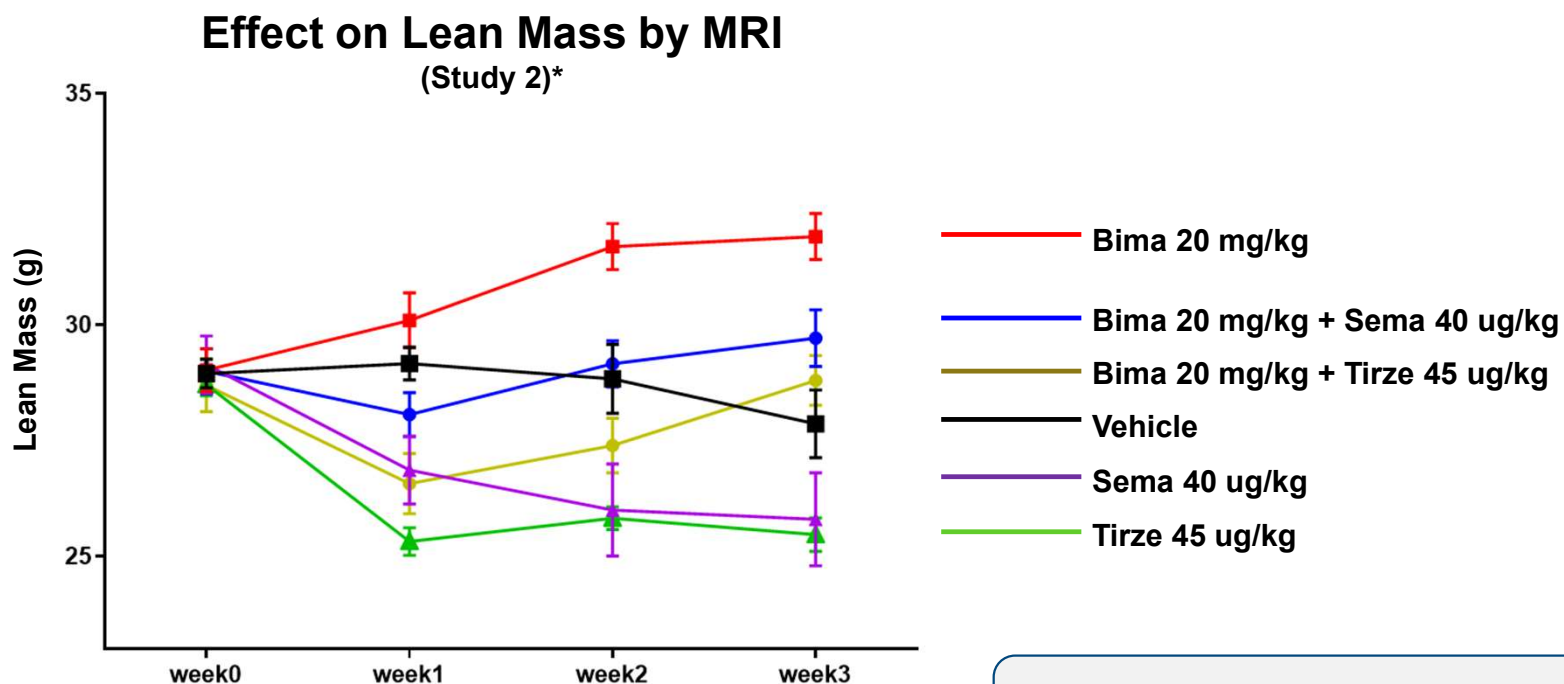
# Effect of murine bimagrumab + incretin treatment on lean mass



- Murine bimagrumab increased lean mass
- Both incretins caused reduction in lean mass (~9% vs. vehicle)

\*Similar results seen in study 1 with murine bimagrumab and semaglutide on terminal measurement of gastrocnemius muscle weight

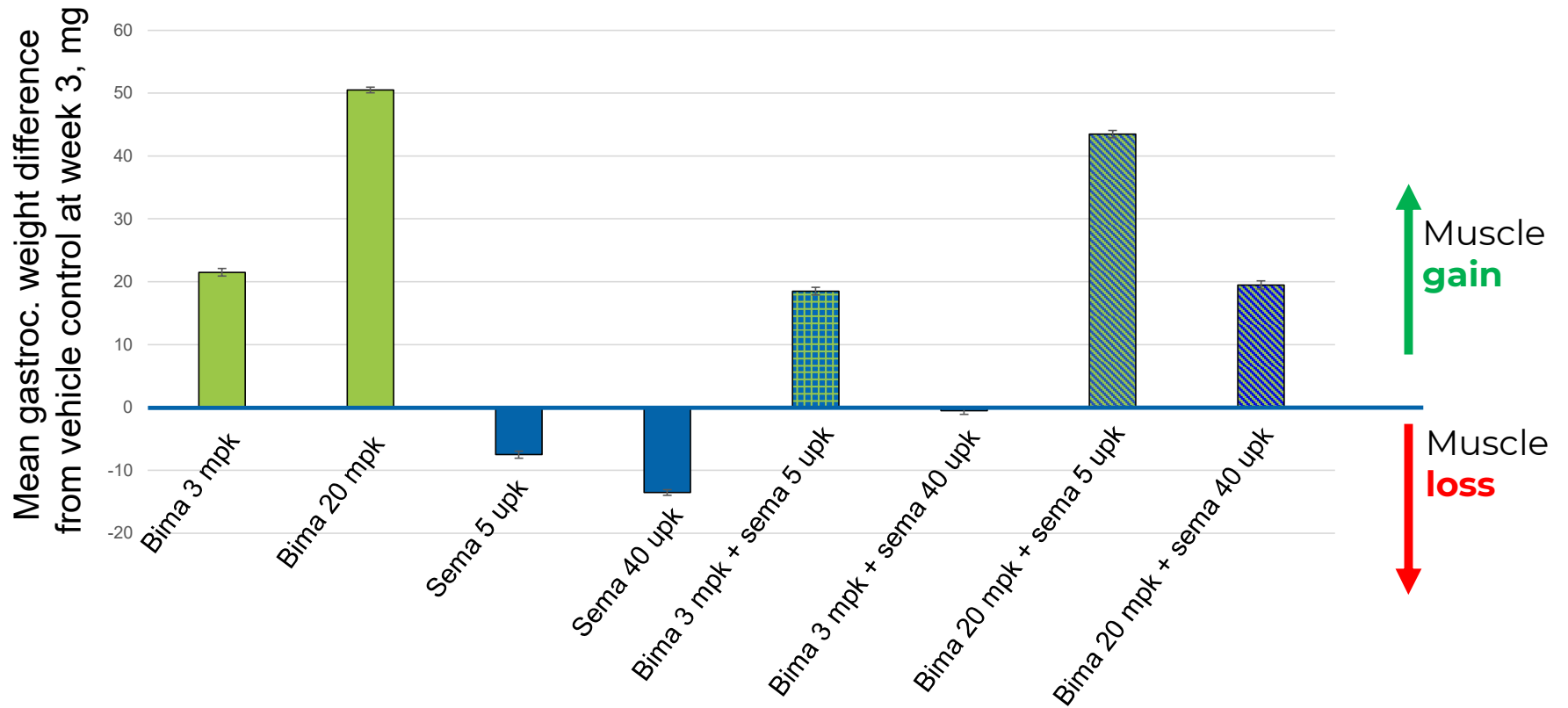
## Effect of murine bimagrumab + incretin treatment on lean mass



*Murine bimagrumab rescued lean mass loss induced by both semaglutide and tirzepatide*

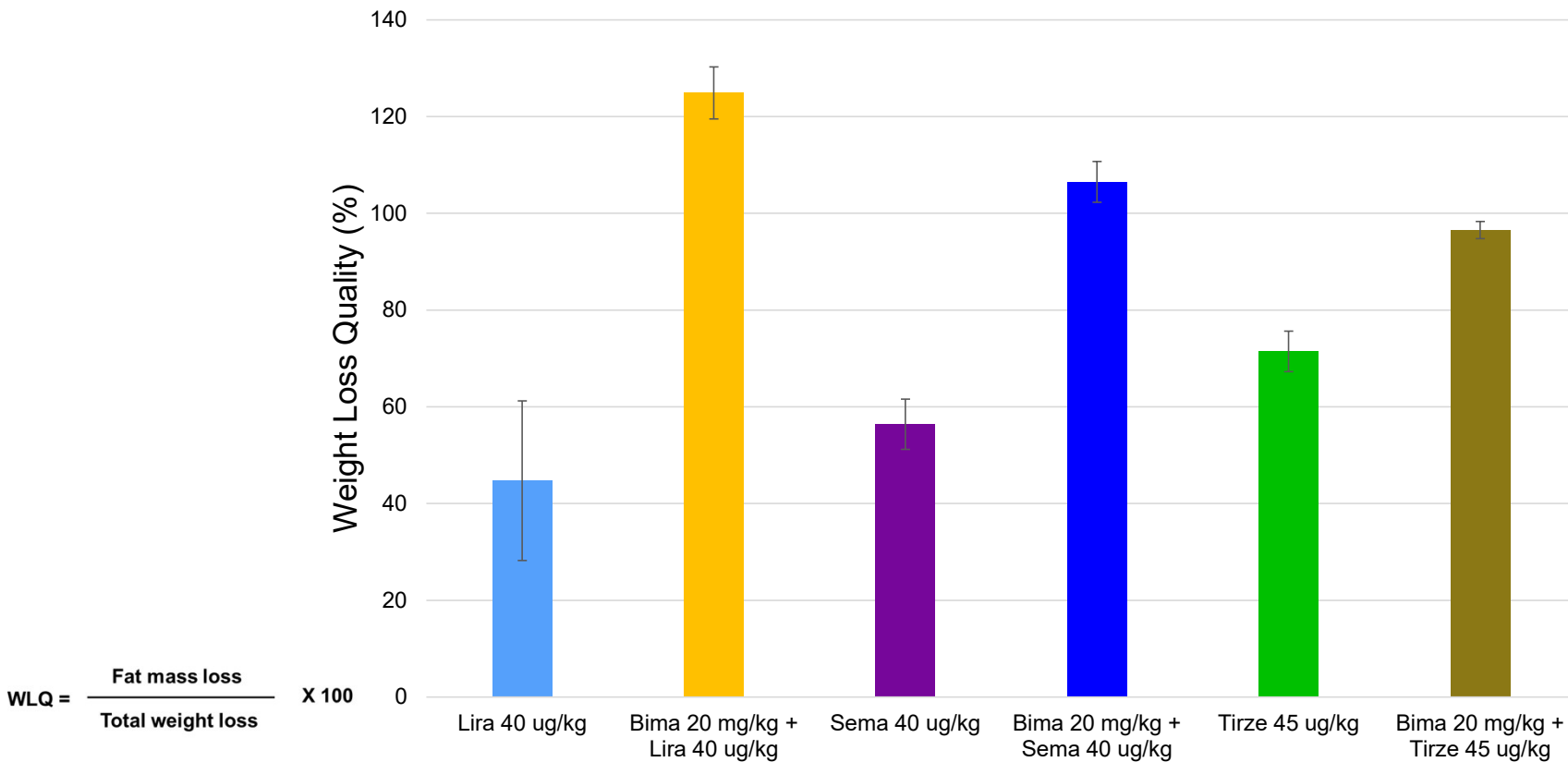
\*Similar results seen in study 1 with murine bimagrumab and semaglutide on terminal measurement of gastrocnemius muscle weight

# Muscle mass changes in DIO mice reflect lean mass changes



Vehicle controls mean gastroc. weight 332.5 (+/- 4.4) mg

## Addition of bimagrumab to incretins improved weight loss quality in DIO mice



## Expected benefits of improved weight loss quality

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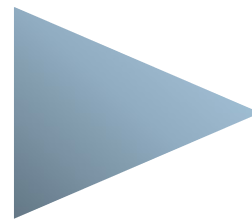
- Resistance to weight re-gain upon discontinuation of therapy
- Sustained improvement in insulin sensitivity
- Superior body composition outcome



## Conclusions: bimagrumab + incretins in the mouse DIO model

- Incretin agonists and murine bimagrumab are additive with respect to fat mass loss
- Murine bimagrumab was able to reverse/prevent the muscle mass loss caused by incretin agonists when the drugs were co-administered and weight loss amount and quality were superior in the combination groups
- No adverse consequences of the drug combinations were evident

These DIO mouse model studies supported the investigation of bimagrumab + semaglutide combination in humans



**BELIEVE**

**Phase 2b clinical study ongoing  
NCT05616013**

# Acknowledgements

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- Thank you for your attention!