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# CNS-Penetrant NLRP3 Inhibitor VTX3232

## Results of Diet-Induced Obese Mouse Model Studies

**June 2024**

# Forward Looking Statements

Ventyx Biosciences, Inc. ("Ventyx" or the "Company") cautions you that statements contained in this presentation regarding matters that are not historical facts are forward-looking statements. These statements are based on the Company's current beliefs and expectations. Such forward-looking statements include, but are not limited to, statements regarding: the design and optimization of VTX3232 for CNS-efficacy, including its potency and selectivity as well as its pharmacokinetic, pharmacodynamic and safety profile; the potential of VTX3232 to drive weight loss through NLRP3 inhibition, whether alone or in combination with GLP-1 receptor agonists; the potential for VTX3232 to potently inhibit NLRP3 in the cerebral spinal fluid; the anticipated timing for the initiation of Phase 2 trials of VTX3232; the anticipated timing of reporting results from Phase 2 trials of VTX3232; and the trial design of any Phase 2 trials of VTX 3232, including the endpoints of the studies, the biomarkers to be studied, and the inclusion of any other pharmaceutical drug products in the studies.

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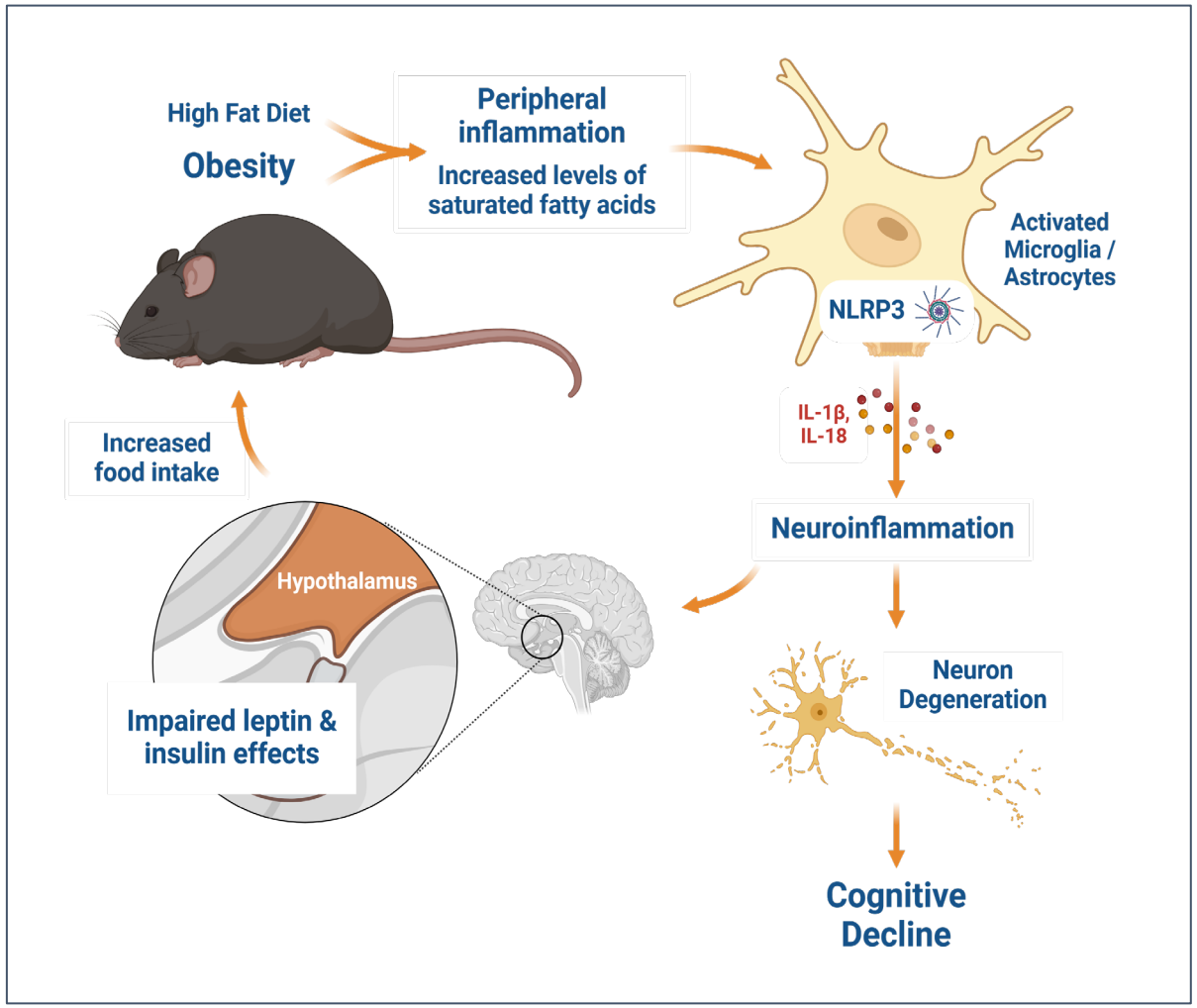
# The Role of NLRP3 in Obesity: Building a Weight of Evidence…

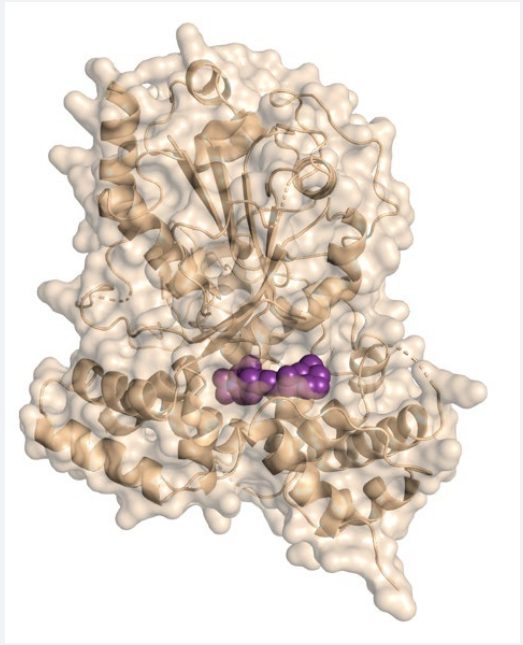
- The NLRP3 inflammasome is emerging as an important axis in obesity and obesity-related cardiometabolic diseases
  - Obesity is a chronic inflammatory condition associated with microglial activation and release of NLRP3-related cytokines including IL-1β and IL-6
  - Reactive gliosis (inflammation) in the hypothalamus proposed as potential mechanism[1]
  - Calorie restriction and exercise-mediated weight loss in obese individuals associated with reduced expression of NLRP3 and decreased systemic inflammation[2]
- In preclinical studies, NLRP3 activation is associated with obesity-related insulin resistance[2]
- NLRP3 inhibition drives weight loss in a diet-induced obesity (DIO) mouse model[3]




1. Thaler et al., *J Clin Invest*. 2012;122(1):153–162.; 2. Vandanmagsar et al., *Nat Med*. 2011 Feb;17(2):179-88.; 3. Thornton et al., *Journal of Pharmacology and Experimental Therapeutics* Feb 9, 2024. Figure adapted from Van Dyken and Lacoste *Front Neurosci* 2018.

# VTX3232: Novel CNS-Penetrant NLRP3 Inhibitor

## Phase 2 Ready for Neuroinflammatory Diseases and Conditions



**Rapid equilibration** across BBB to reach microglial target cells

### Rationally Designed and Optimized for CNS-Efficacy

**Highly Potent and Selective**

- Hu WB $IC_{50}$ (IL-1β) = **15 nM**
- Mu WB $IC_{50}$ (IL-1β) = **94 nM**
- **Inhibits palmitate-induced IL-1β**
- No inhibition of other inflammasomes

**Optimal PK, PD and Safety Profile**

- Good safety & tolerability in Phase 1 Study
- Equal CNS partitioning; **human Kp,uu = 0.5**
- T½ = ~17 h with high free-drug fraction
- Robust effects on inflammatory biomarkers

**QD dosing can achieve potent NLRP3 inhibition in the CSF**

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Source: Ventyx internal data. BBB, blood brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; Kp,uu, partition coefficient. Images created with BioRender.

# VTX3232 Preclinical Studies in Diet-Induced Obese (DIO) Mice

**Two 28-day studies completed in DIO mice:**

- **Study 1:** VTX3232 and semaglutide monotherapy
- **Study 2:** Addition of VTX3232/semaglutide combination

**Key takeaways from both studies:**

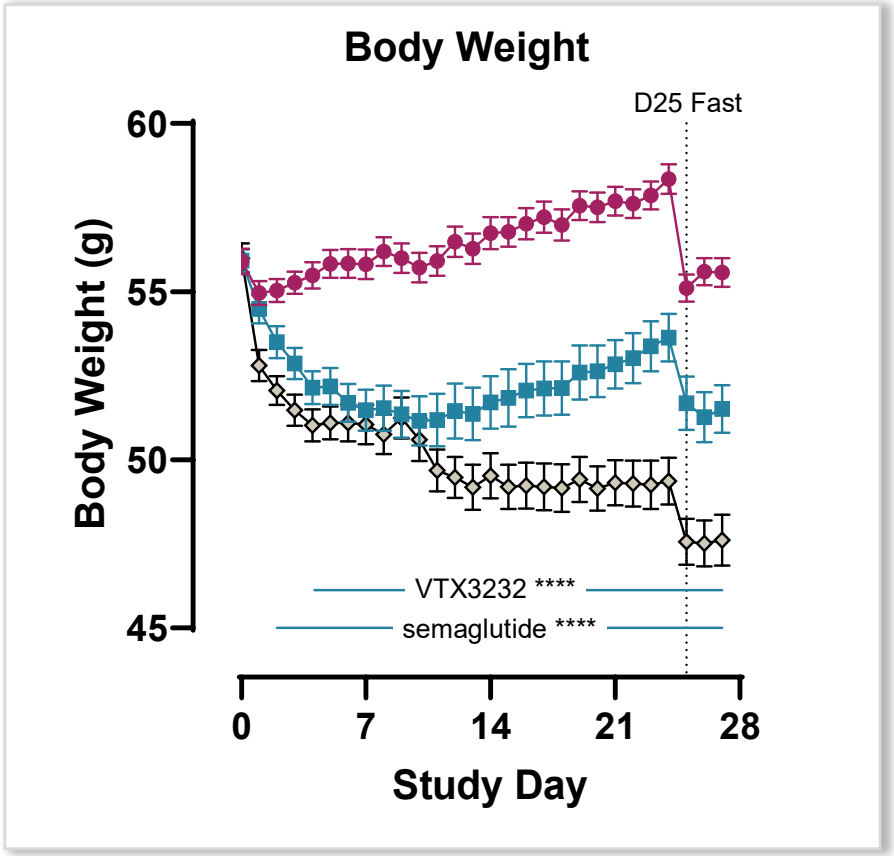
## VTX3232 monotherapy

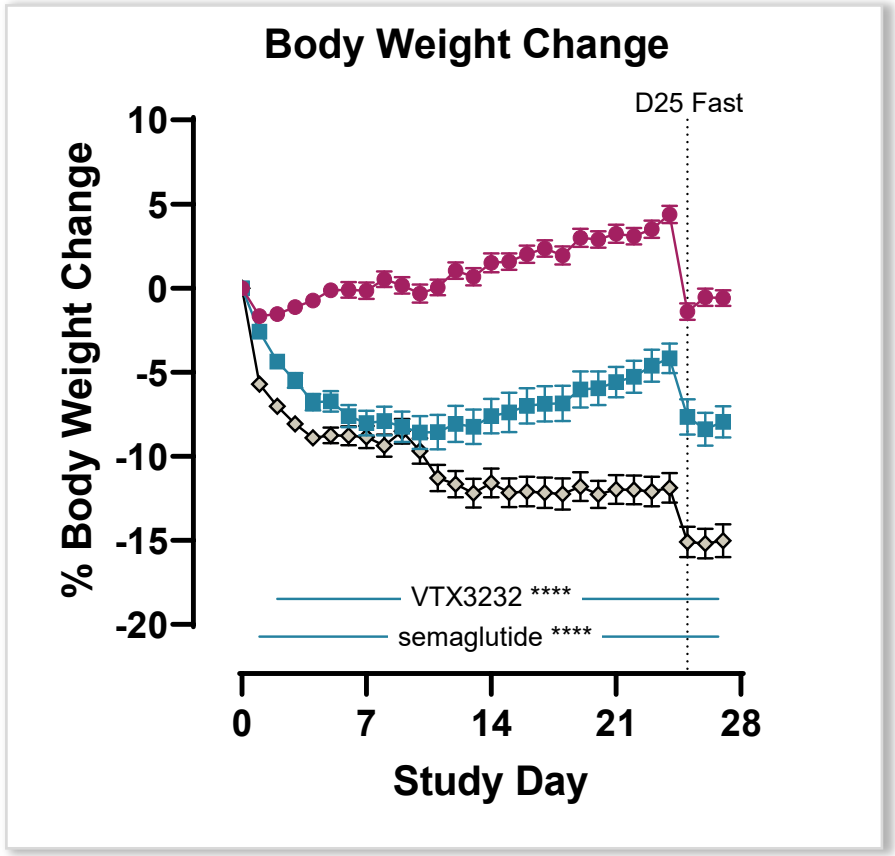
- Decreases body weight and food intake
- Reduces systemic inflammatory markers
- Depletes liver fat and restrains triglyceride level increases
- Decreases cholesterol levels
- Decreases insulin resistance, hyperglycemia and hemoglobin A1c

## VTX3232 combination with semaglutide

- Additive reductions on body weight and food intake
- Greater reduction of systemic inflammatory markers
- Improves body composition towards a greater proportion of lean mass
- Incremental improvements in markers of metabolic dysfunction

# VTX3232 Reduces Body Weight in DIO Mouse Model



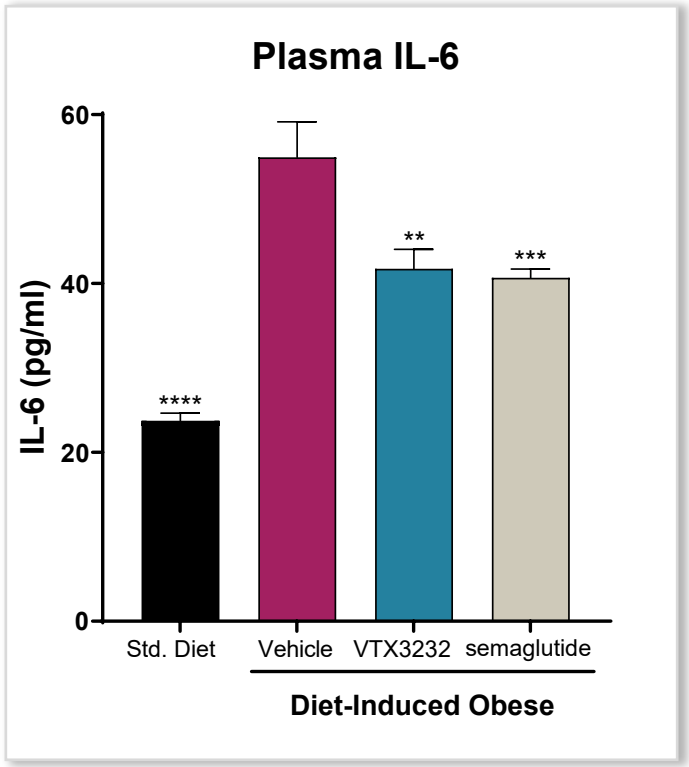

**VTX3232 decreases body weight by 5g (~9%) vs. DIO Vehicle**

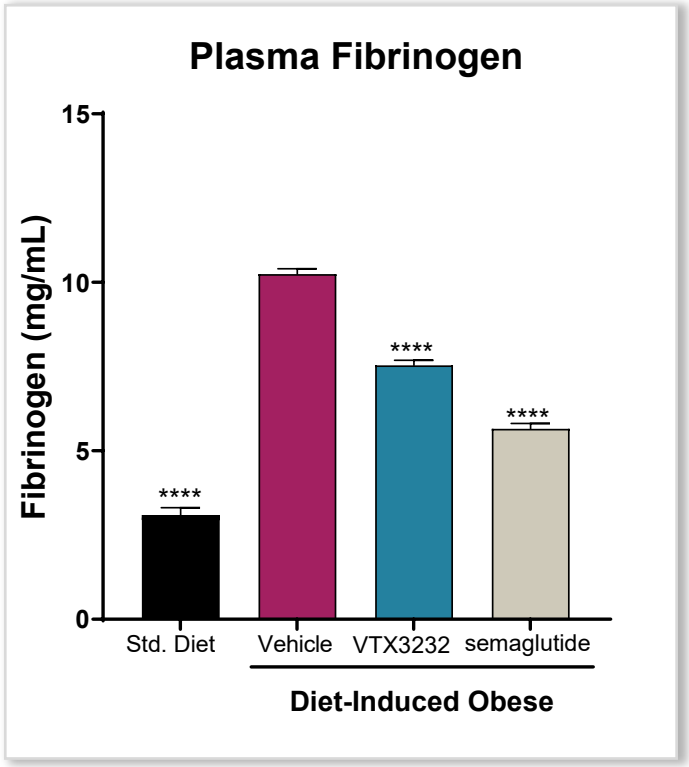
DIO-Vehicle
DIO-VTX3232
DIO-sema

VTX3232 20 mg/kg BID orally; semaglutide 10 μg/kg QD subcutaneously; mean ± SEM, ****p<0.0001 vs DIO Control; repeated measures ANOVA, Dunnett's post-hoc; semaglutide decreases body weight by ~9g (~16%)

# VTX3232 Reduces DIO-Driven Inflammatory Markers and Acute Phase Proteins in DIO Mouse Model

## Fibrinogen expression induced by IL-1β-sensitive cytokine IL-6

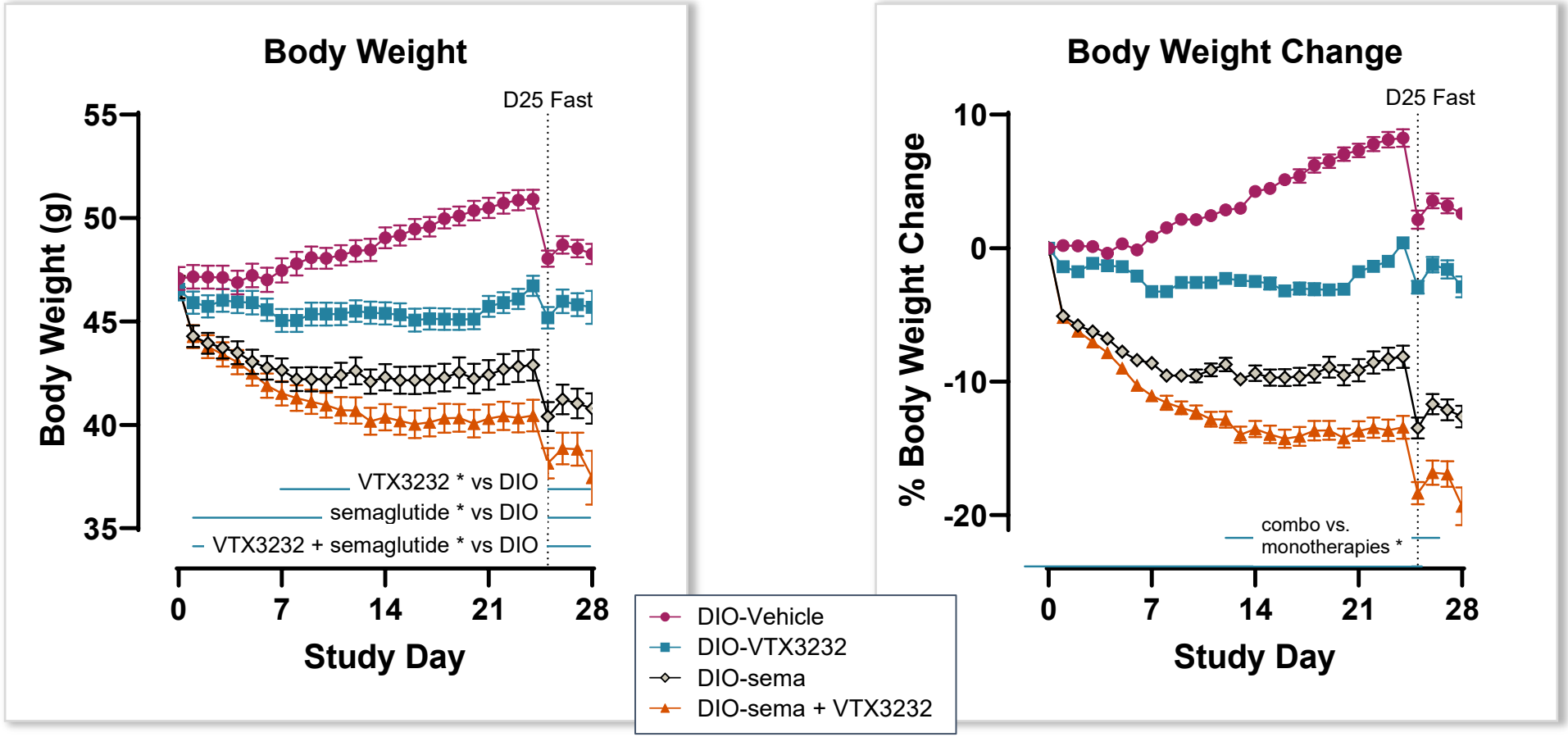

**Reduction in circulating cytokines IL-1β, IL-6**

**Reduction in DIO-driven fibrinogen**

VTX3232 20 mg/kg BID orally; semaglutide 10 μg/kg QD subcutaneously; mean ± SEM, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, 1-way ANOVA, Dunnett's post hoc
High sensitivity C-reactive peptide was measured but not elevated in DIO mice.

# VTX3232 + Semaglutide Combo Shows Greater Body Weight Change (%) than Semaglutide Alone

## VTX3232 Remains Effective as Monotherapy in Study 2

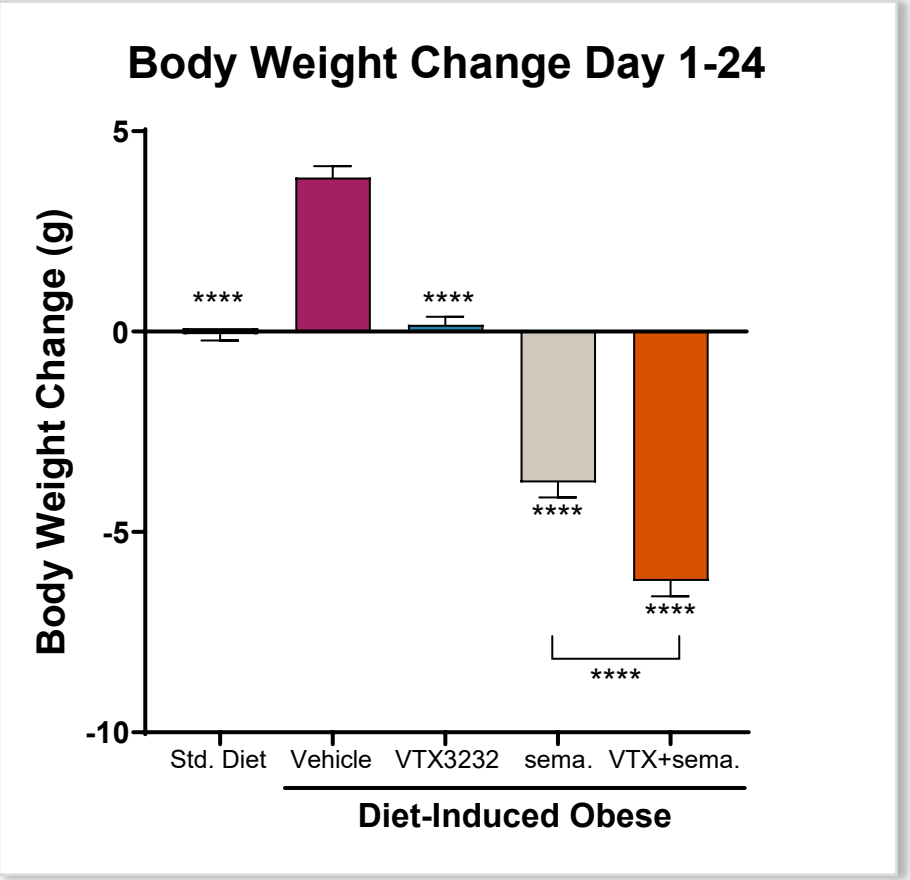


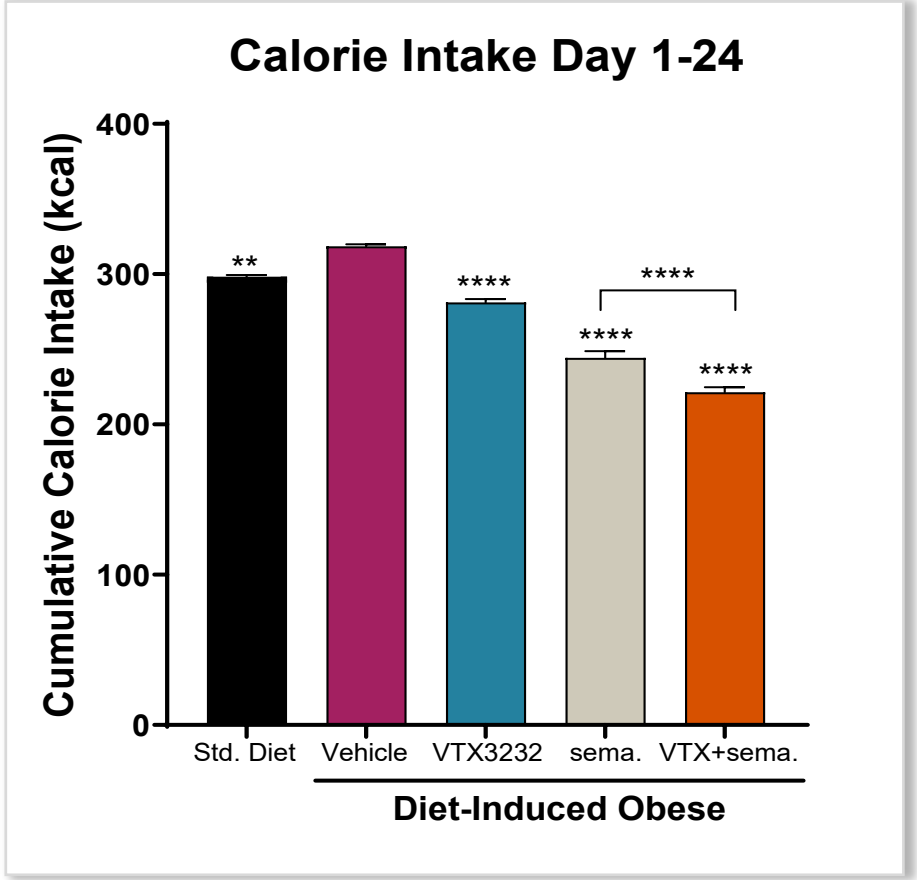

**VTX3232[1] and semaglutide[2] combination decreases body weight by 10.5g (~22%) vs. vehicle**

VTX3232 20 mg/kg BID orally; Semaglutide 10 μg/kg QD subcutaneously; mean ± SEM, * p <0.05 or more highly significant at all indicated timepoints, Mixed effects ANOVA, Sidak's post-hoc test. [1]VTX3232 monotherapy decreases body weight by ~4g (~8%), [2]Semaglutide monotherapy decreases body weight by ~8g (~16%)

# VTX3232 + Semaglutide Combo Shows Greater Reduction in Body Weight Gain and Caloric Intake Relative to Semaglutide Alone

## VTX3232 Remains Effective as Monotherapy in Study 2

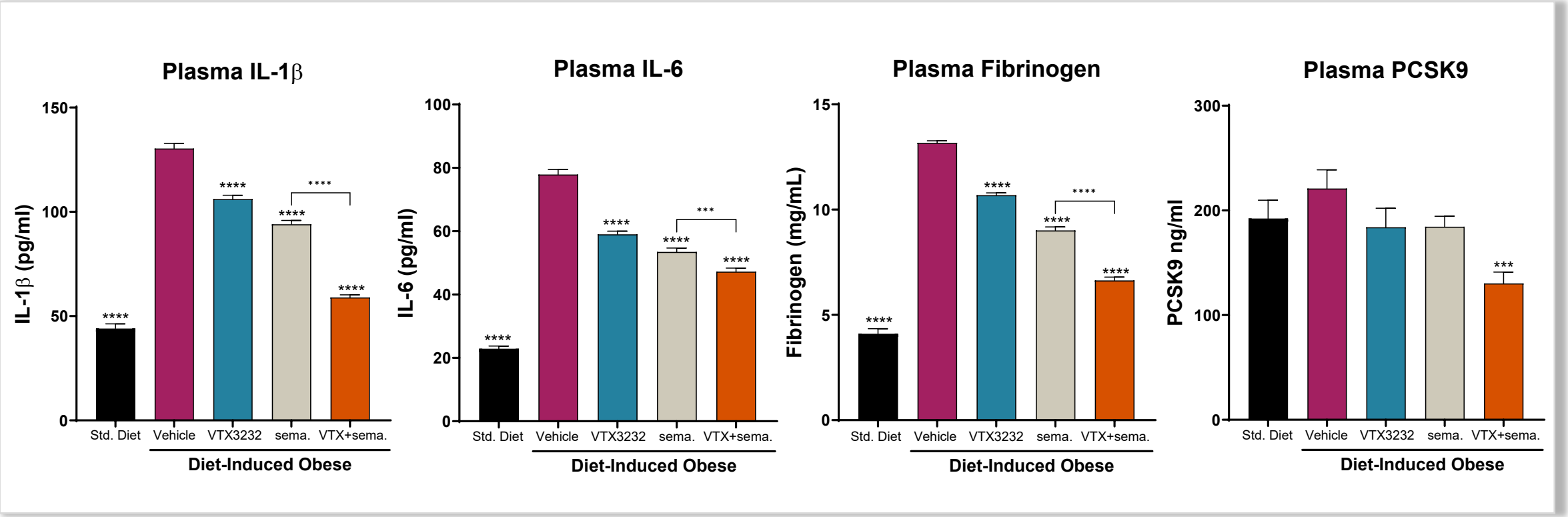



**VTX3232 and semaglutide combination suppresses BWG and food intake more than either monotherapy**

sema., semaglutide; Std., standard; VTX, VTX3232; BWG, body weight gain; 1-way ANOVA with Sidak's multiple comparison test to DIO Vehicle and the combination group to semaglutide monotherapy; key comparisons only are noted on graphs; **p<0.01, ***p<0.001, ****p<0.0001

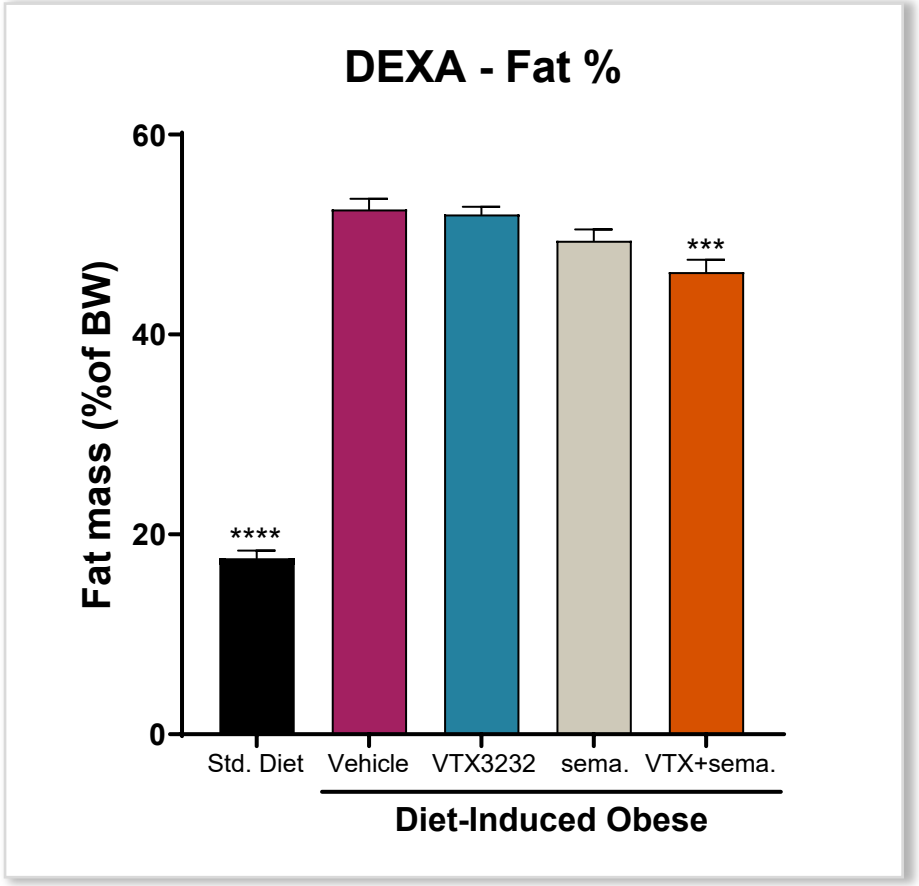
# Combination of VTX3232 and Semaglutide Reduces Inflammatory Risk Factors More than Either Monotherapy

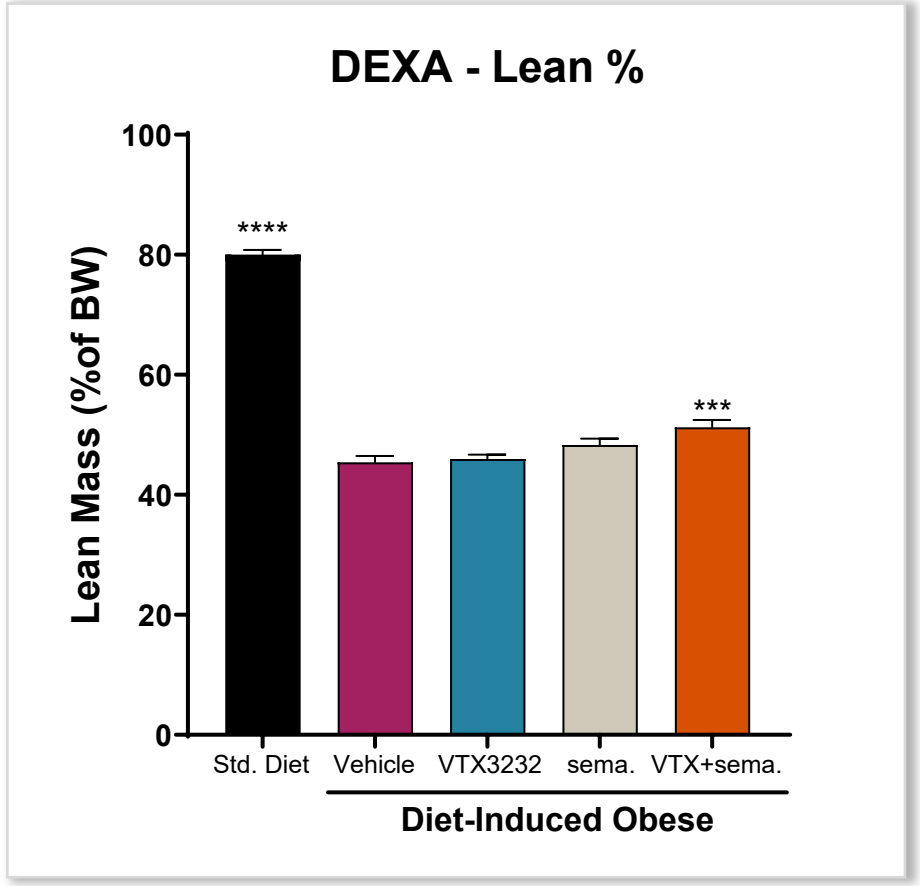



- VTX3232 and semaglutide monotherapies decrease IL-1β, IL-6 and fibrinogen
- Combination therapy lowers inflammatory CV risk markers better than either monotherapy

One-way ANOVA, Sidak's post hoc test ***p<0.001, ****p<0.0001

# Combination of VTX3232 and Semaglutide Improves Body Composition

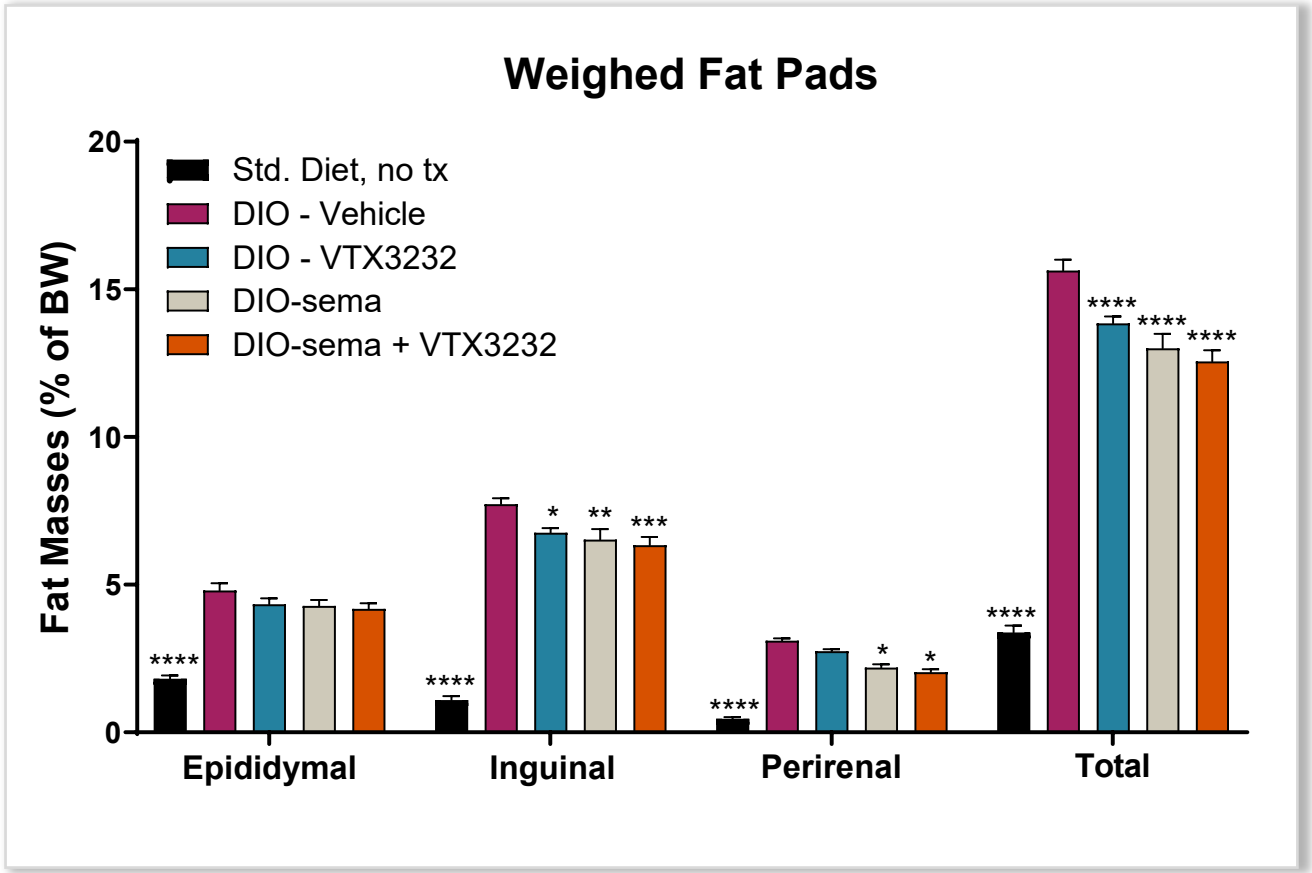


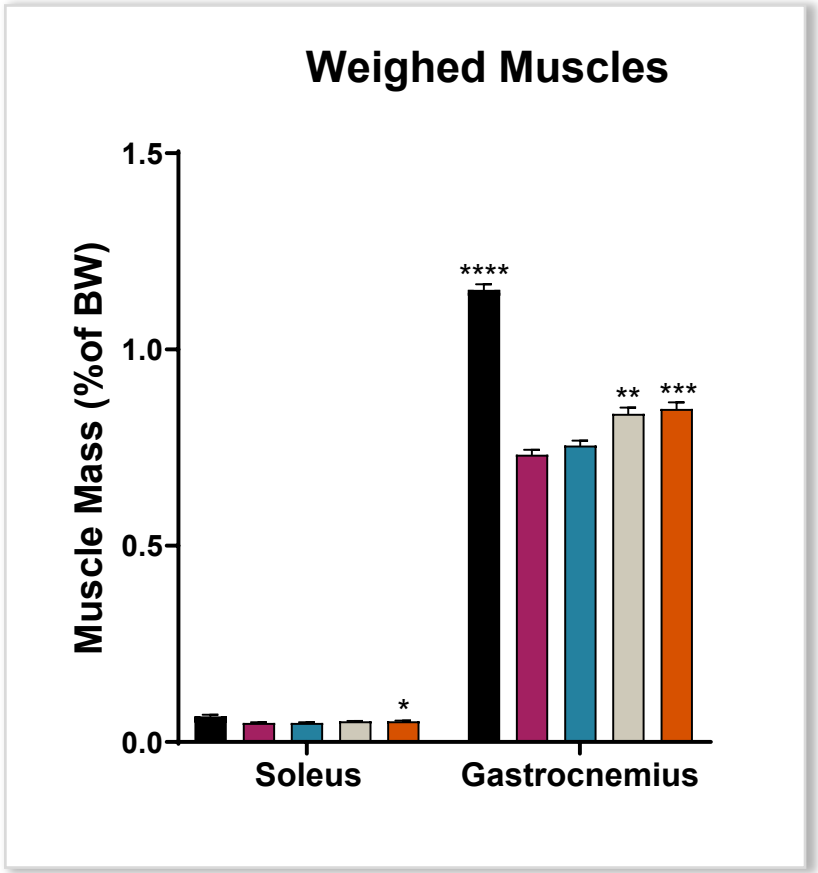




**VTX3232 and semaglutide combination decreases relative fat mass and increases relative lean mass**

DEXA, dual energy X-ray absorptiometry, Bone mineral content mass not represented; 1-way ANOVA, Sidak's post-hoc test ***p<0.001, ****p<0.0001

# Combination of VTX3232 and Semaglutide Incrementally Improves Body Composition

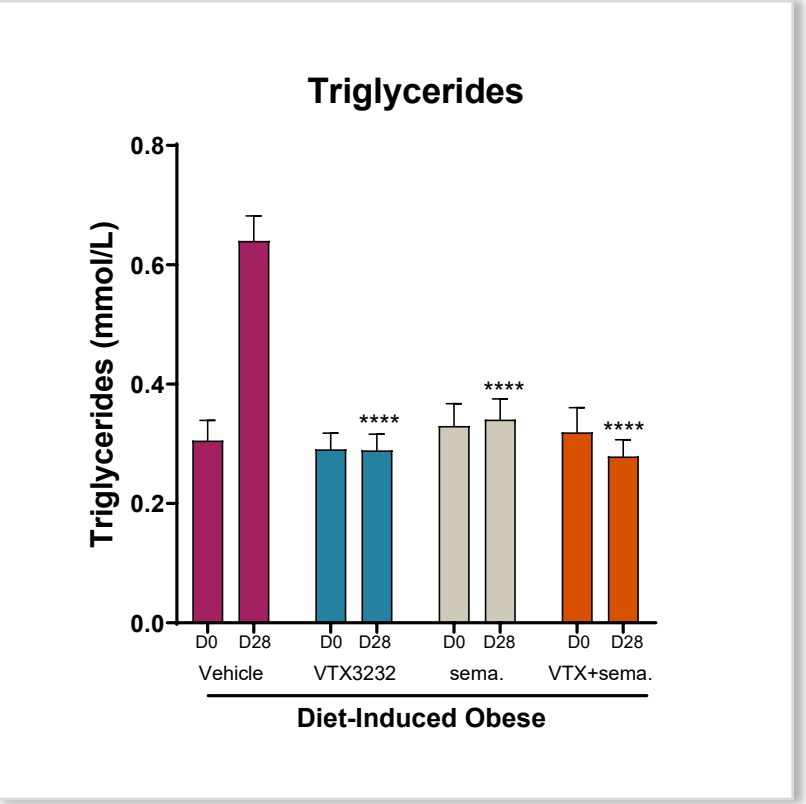


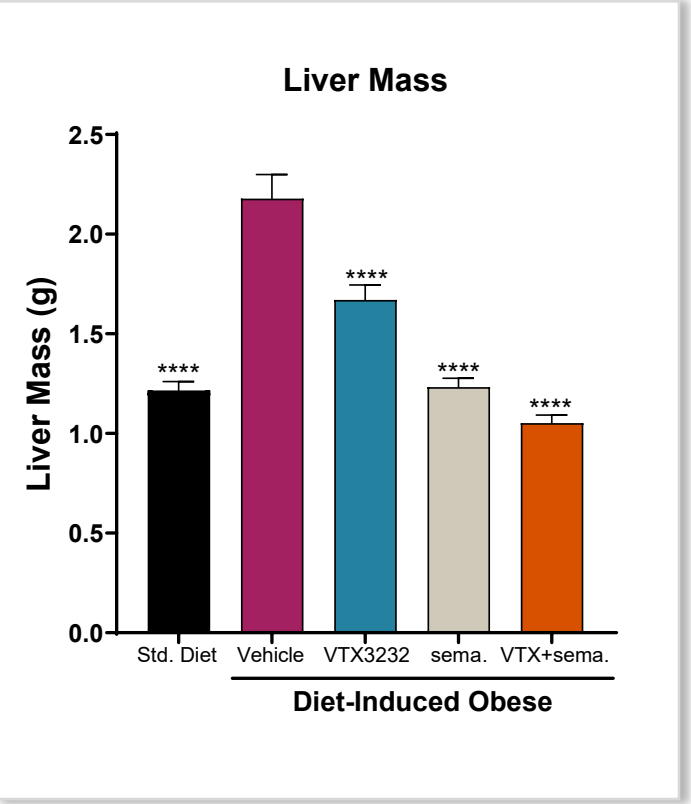



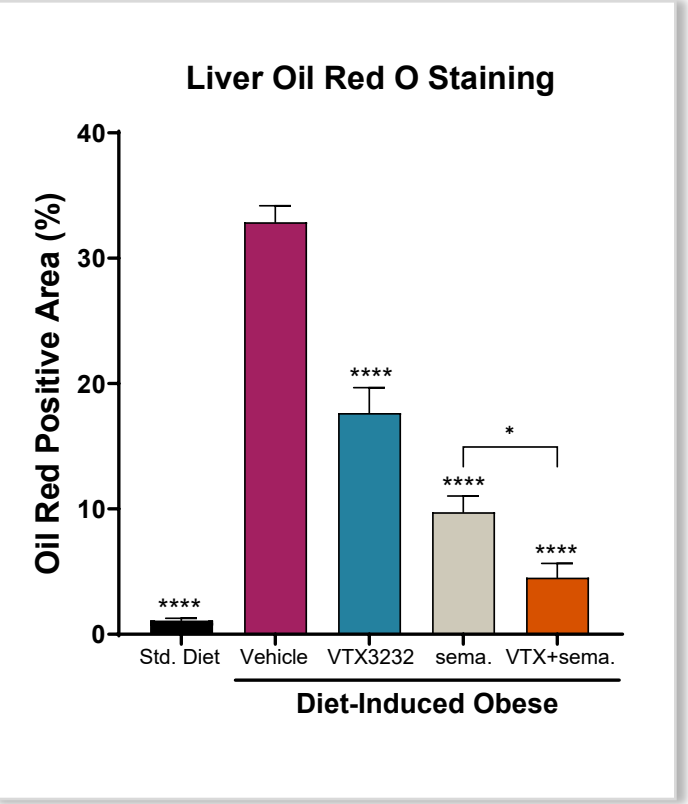

**VTX3232 and semaglutide monotherapy and combined therapy decrease fat pad weight and increase gastrocnemius weight**

Total is the sum of the specific fat mass weights; 1-way ANOVA, Sidak's post-hoc test *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

# VTX3232 and Semaglutide Combination Shows Greater Improvement in Liver Steatosis Relative to VTX3232 or Semaglutide Alone



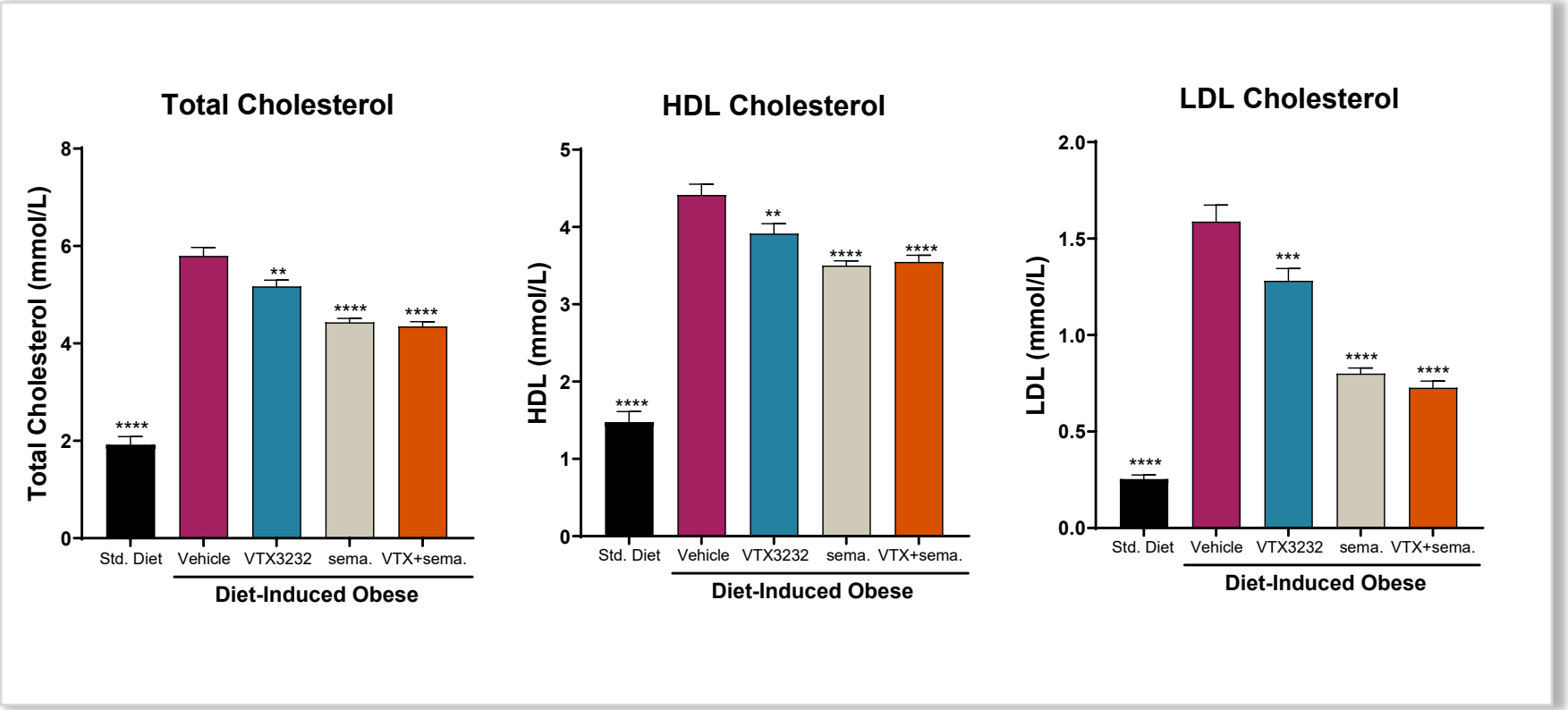




- **VTX3232** reduces liver mass and restricts increases in plasma triglyceride levels
- **VTX3232 and semaglutide combination** results in lower steatosis and lower mean liver mass than either monotherapy

2-way ANOVA, Dunnett's post-hoc test (triglycerides); 1-way ANOVA, Sidak's post-hoc test *p<0.05, ****p<0.0001

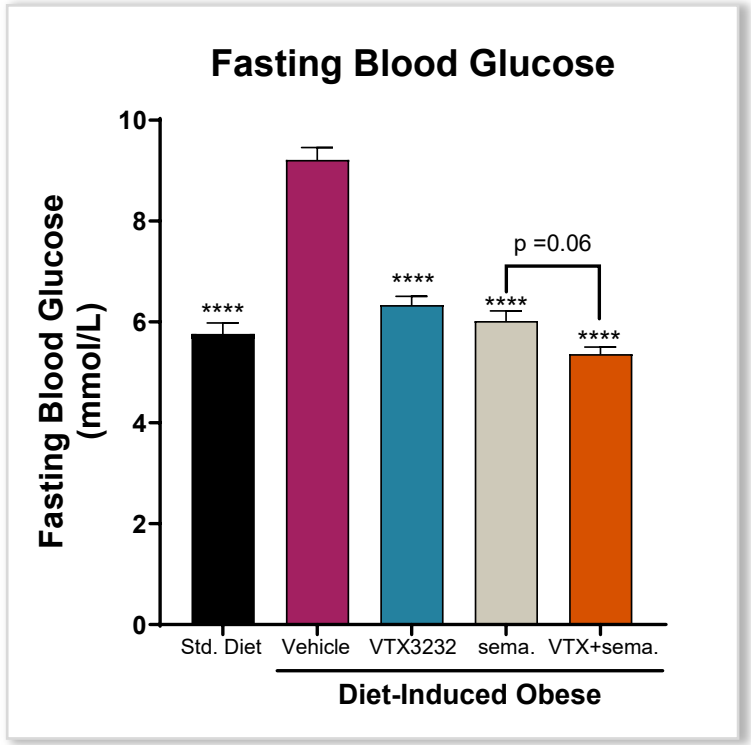
# VTX3232 Reduces Cholesterol in DIO Mice

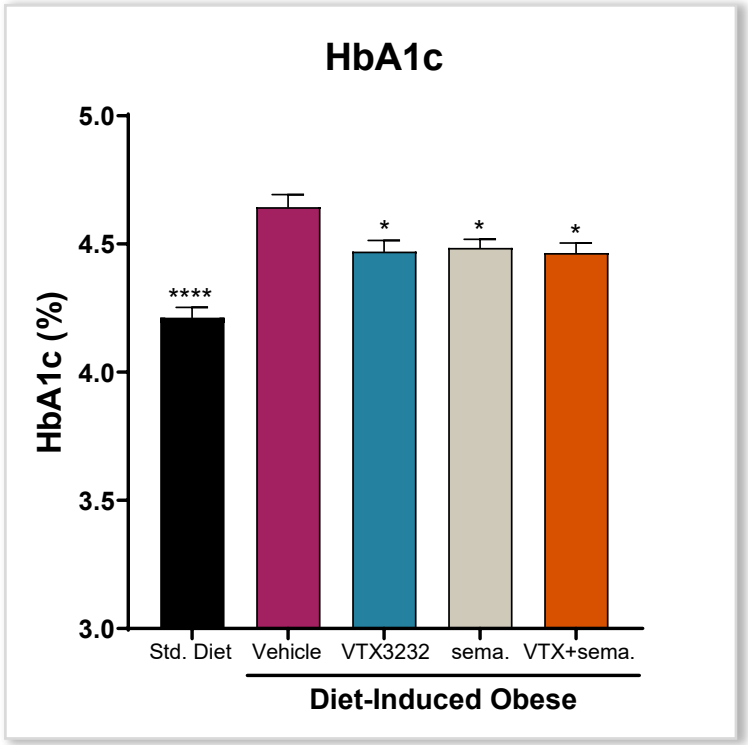



**VTX3232 and semaglutide monotherapy or combination significantly reduces total, HDL and LDL cholesterol**

1-way ANOVA, Sidak's post-hoc test **p<0.01, ***p< 0.001, ****p<0.0001

# Combination of VTX3232 and Semaglutide Incrementally Improves Insulin Resistance


## VTX3232 Monotherapy

- Reduces insulin resistance (HOMA-IR)
- Reduces fasting glucose
- Reduces HbA1c

## VTX3232 and Semaglutide Combination

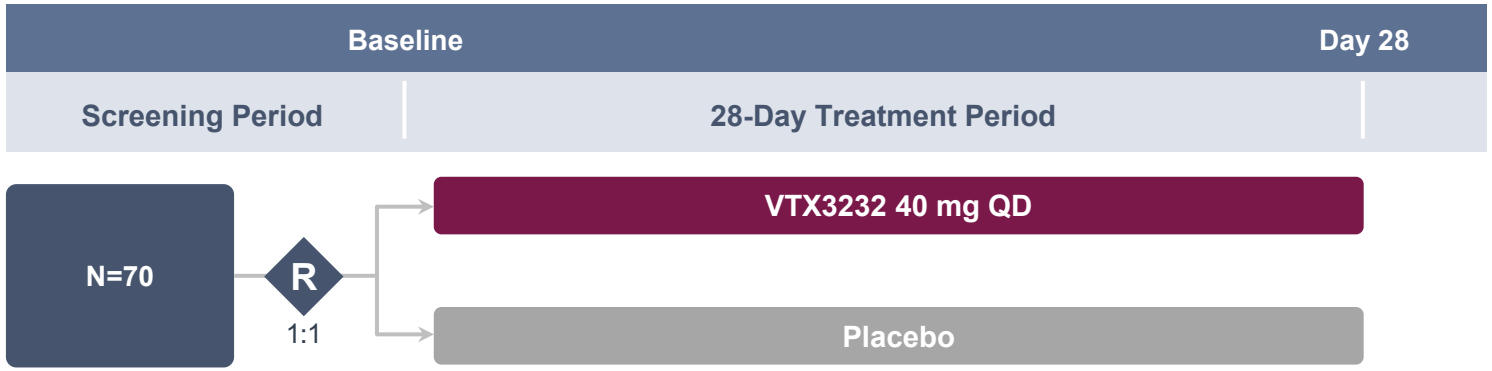
- Lowers mean HOMA-IR and fasting glucose relative to monotherapy

HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance:1-way ANOVA, Sidak's post-hoc test **p<0.01, ***p< 0.001, ****p<0.0001

# Looking Beyond Mice: Studies with VTX3232 in Obese Participants

- **Proof-of-concept Phase 2a trial in participants with obesity expected to initiate in H2 2024**
  - Endpoints include biomarkers of inflammation (hsCRP, IL-1β, IL-18, IL-6, SAA) and cardiometabolic readouts (lipids, glycemic measurements)
  - Assess potential impact on body weight in a short-duration study
  - Topline results expected in **H1 2025**
- **Planning longer Phase 2 trial for initiation H1 2025**
  - 12-week trial of VTX3232 in participants with obesity
  - Primary endpoint: weight loss with VTX3232
  - Potential to include a combination arm with a GLP-1R agonist
  - Inflammation and cardiometabolic biomarkers

## VTX3232 Proposed Phase 2a Trial in Obese Participants*




*Preliminary Phase 2a trial design, subject to change.