# ASC47, An Adipose-Targeted, Muscle-Preserving Weight Loss Drug Candidate For Obesity, Demonstrated Significant Weight Loss And Preserved Muscle In DIO Mice

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# Disclosure

**Dr. Jinzi Jason Wu is an employee of Ascletis Pharma (China) Co., Limited, Hong Kong**

# Overview of ASC47

- ASC47 is a thyroid hormone receptor β (THRβ) selective small molecule agonist.

- ASC47 was designed with unique and differentiated properties to enable targeted delivery to adipose tissue.

- ASC47 is a muscle-preserving weight loss drug candidate to treat obesity.

- ASC47 demonstrated a half-life of up to 26 days and 40 days, respectively, in Phase Ib subcutaneous injection studies in healthy subjects and participants with obesity, supporting once-monthly to once-bimonthly administration.

For more details, please visit our official website: *https://www.ascletis.com*

# ASC47 is133-fold more potent than resmetirom *in vitro*

**Binding activity of ASC47 to THRβ by TR-FRET**



| Compound ID | EC$_{50}$ (μM) |
|---|---|
| Resmetirom | 0.133 |
| ASC47 | 0.001 |
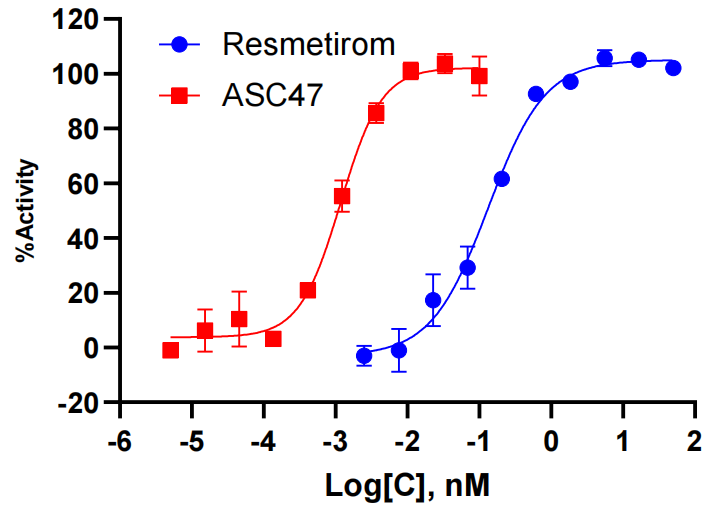
**THRβ selectivity of ASC47 over THRα**

| Compound ID | EC$_{50}$ α (μM) | EC$_{50}$ β (μM) | β selectivity |
|---|---|---|---|
| Resmetirom | 2.867 | 0.133 | 21.54 |
| ASC47 | 0.0369 | 0.001 | 36.90 |

**ASC47 showed great *in-vitro* activity in binding assay and luciferase reporter assay.**

# Study Design: ASC47 tissue distribution in DIO mice



5-week-old C57BL/6J mice were fed with 60% HFD for 16 weeks

**Treatment:**
**ASC47, 15/45 mg/kg, SQ, Q2W**

**In vivo study period (HFD-maintenance)**

**Termination**

ASC47 were dosed on Day1, Day15 and Day29 as indicated (orange arrow)

**Week -16**

**Week 1/Day1 Start treatment**

**Week6/Day43 Termination**

**Tissue collection**

**Homogenize**

**LC-MS/MS detection**
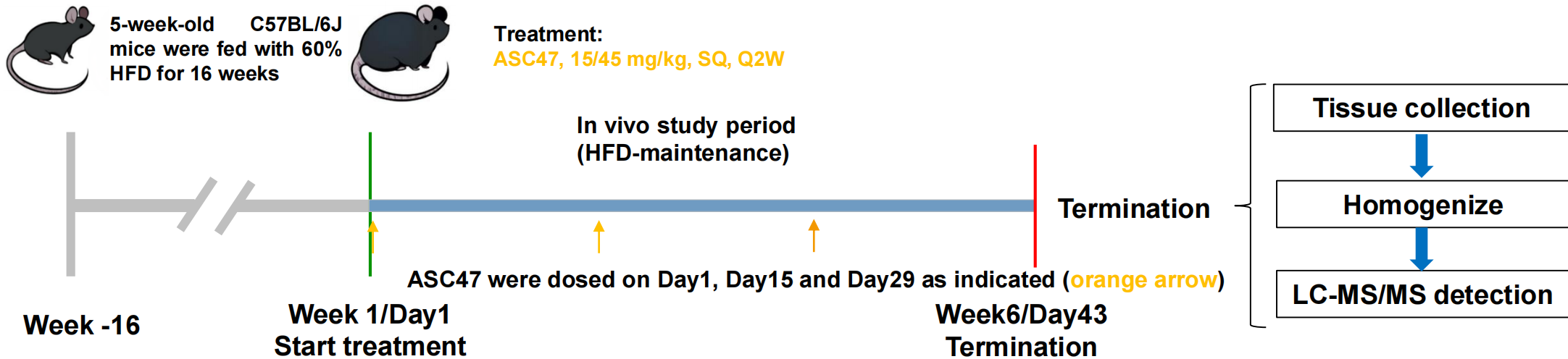
Note:
1. HFD: High Fat Diet
2. SQ: Subcutaneous(ly)
3. Q2W: Every two weeks
4. DIO mice: Diet-induced obese mice

# ASC47 is an adipose-targeted THRβ small molecule agonist



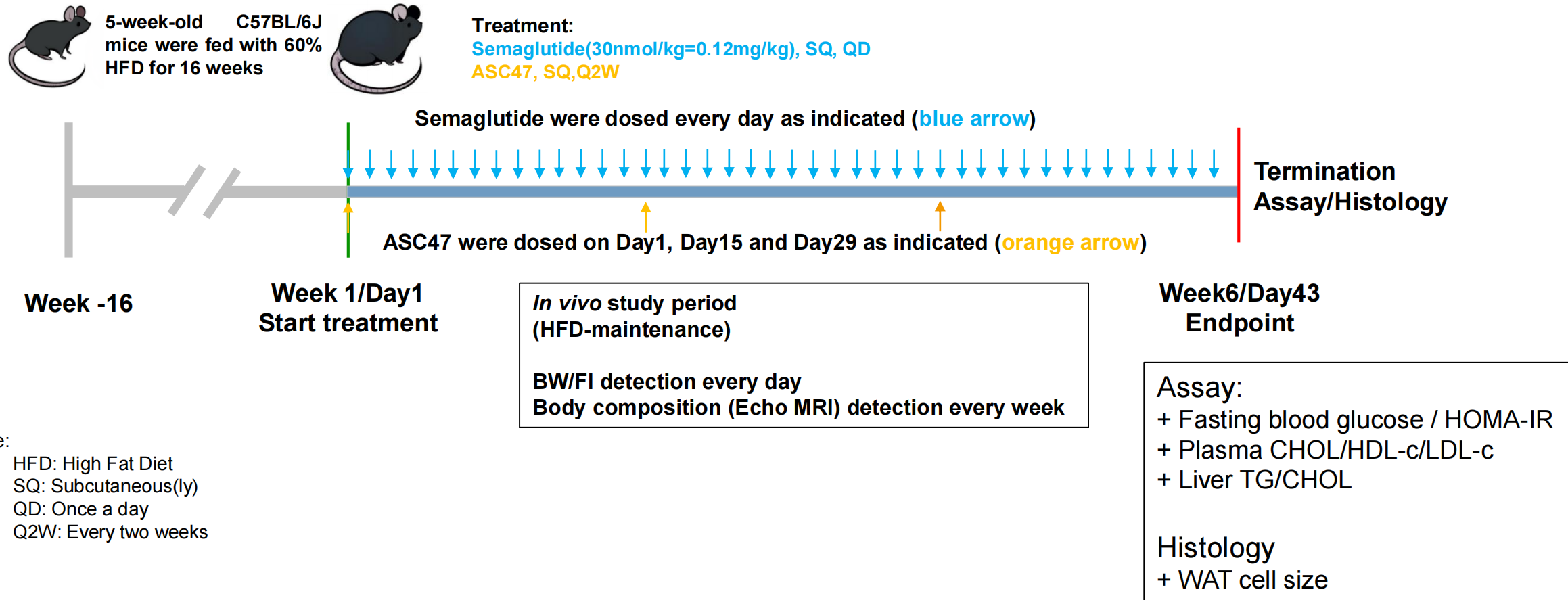**Inguinal WAT**

**Epididymal WAT**

**Liver**

- ☐ DIO, ASC47(15 mg/kg), Q2W, SQ
- ☐ DIO, ASC47(45 mg/kg), Q2W, SQ

Data were presented as truncated violin plot by Prism GraphPad; N=10.
WAT: White adipose tissue
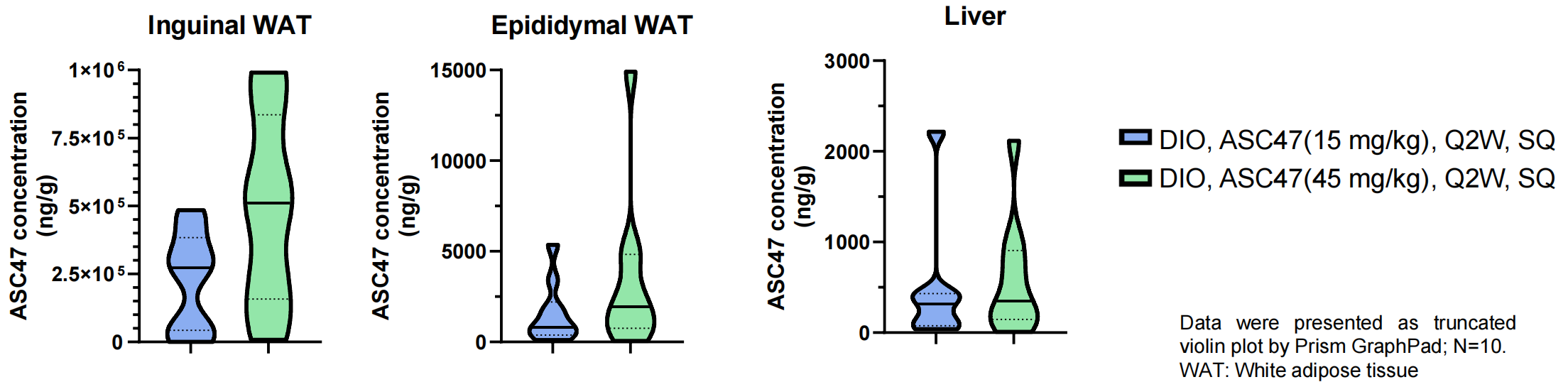
## ASC47 mean concentration in tissues (ng/g)

| Group | 15 mg/kg ASC47 | 45 mg/kg ASC47 |
|---|---|---|
| Inguinal WAT | 225,447 | 488,895 |
| Epididymal WAT | 1,545 | 3,384 |
| Liver | 487 | 585 |

## ASC47 tissue distribution ratio

| Group | 15 mg/kg ASC47 | 45 mg/kg ASC47 |
|---|---|---|
| Inguinal WAT to Liver | 462.9 | 835.7 |
| Epididymal WAT to Liver | 3.2 | 5.8 |

# Study Design: Weight change of ASC47 vs Sema in DIO mice
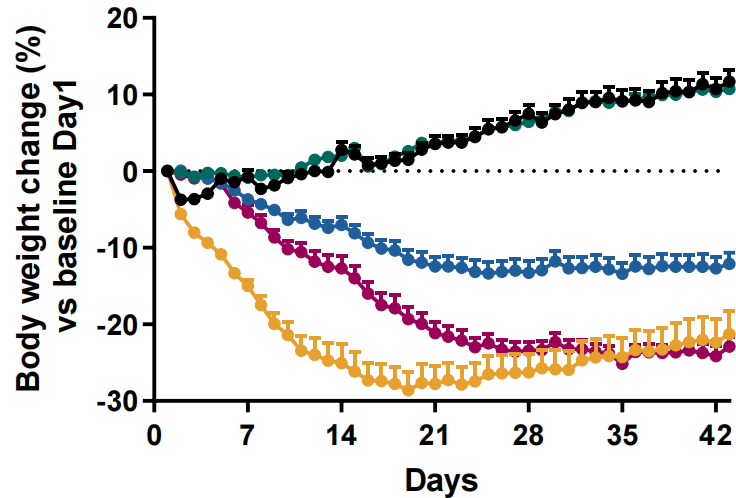
**EASO** European Association for the Study of Obesity

5-week-old C57BL/6J mice were fed with 60% HFD for 16 weeks

**Treatment:**
Semaglutide(30nmol/kg=0.12mg/kg), SQ, QD
ASC47, SQ, Q2W

Semaglutide were dosed every day as indicated (blue arrow)

Termination Assay/Histology

ASC47 were dosed on Day1, Day15 and Day29 as indicated (orange arrow)

**Week -16**

**Week 1/Day1**
**Start treatment**

**Week6/Day43**
**Endpoint**

*In vivo* study period
(HFD-maintenance)

BW/FI detection every day
Body composition (Echo MRI) detection every week

Note:
1. HFD: High Fat Diet
2. SQ: Subcutaneous(ly)
3. QD: Once a day
4. Q2W: Every two weeks

Assay:
+ Fasting blood glucose / HOMA-IR
+ Plasma CHOL/HDL-c/LDL-c
+ Liver TG/CHOL

Histology
+ WAT cell size

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Data were presented as Mean ± SEM, One way ANOVA followed by Tukey test by Prism GraphPad; N=10. **** $p<0.0001$
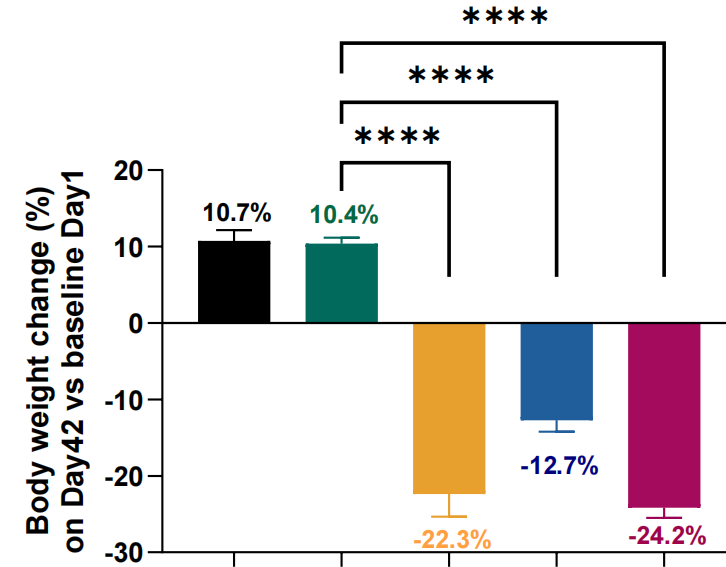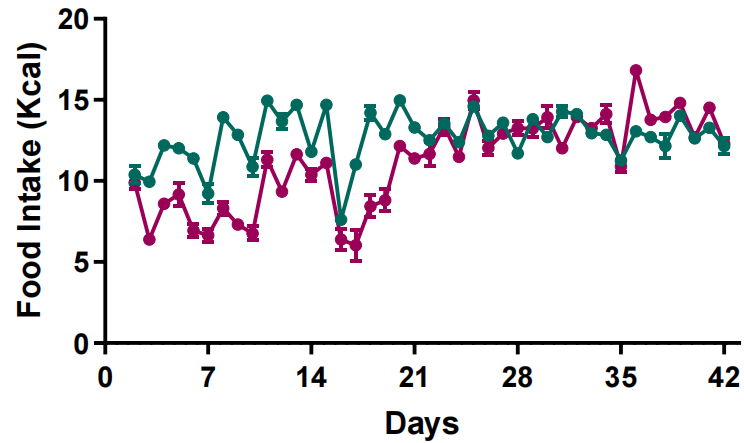
**Total body weight reduction was similar between semaglutide (30nmol/kg, QD) and ASC47 (45mg/kg, Q2W). However, speed of weight loss by ASC47 was lower than semaglutide.**

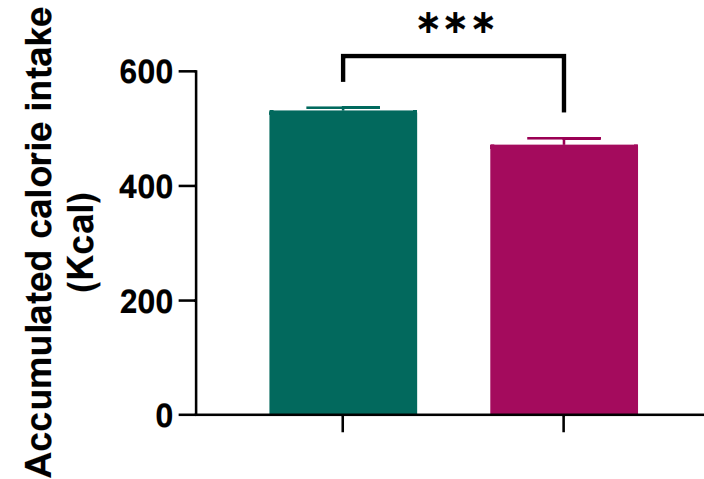# ASC47 to treat obesity: Two major mechanisms of action (MOA)

- **Induce satiety and decrease caloric intake**

- **Preserve muscle and reduce fat**

# ASC47 induced satiety and decreased caloric intake in DIO mice

- DIO, Vehicle, Q2W, SQ
- DIO, ASC47(45 mg/kg), Q2W, SQ

Data were presented as Mean ± SEM, t-test was applied by Prism GraphPad; N=10. *** $p$=0.0001
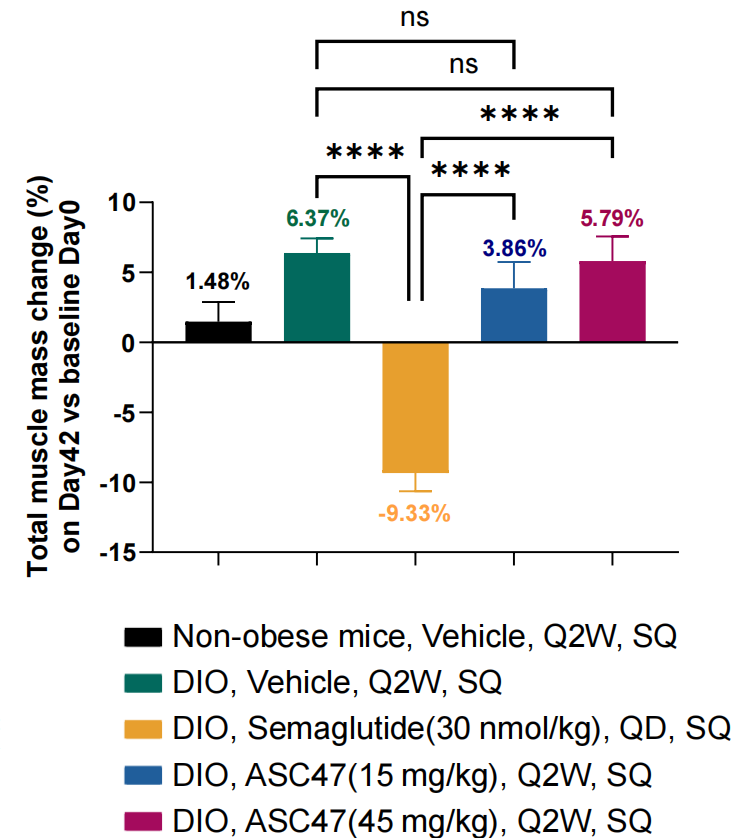
- DIO, Vehicle, Q2W, SQ
- DIO, ASC47(45 mg/kg), Q2W, SQ

**The food intake decreased significantly in ASC47-treated DIO mice (45mg/kg, Q2W).**

# ASC47 preserved muscle while semaglutide reduced muscle
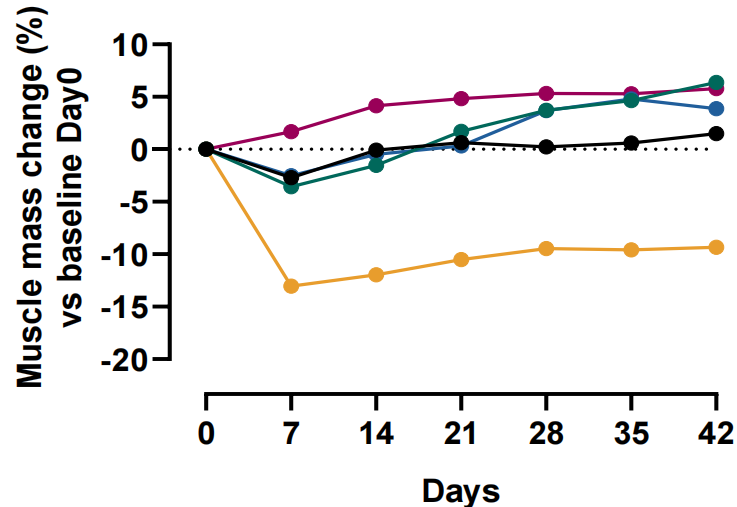


Data were presented as Mean ± SEM, One way ANOVA followed by Tukey test by Prism GraphPad; N=10. **** $p<0.0001$
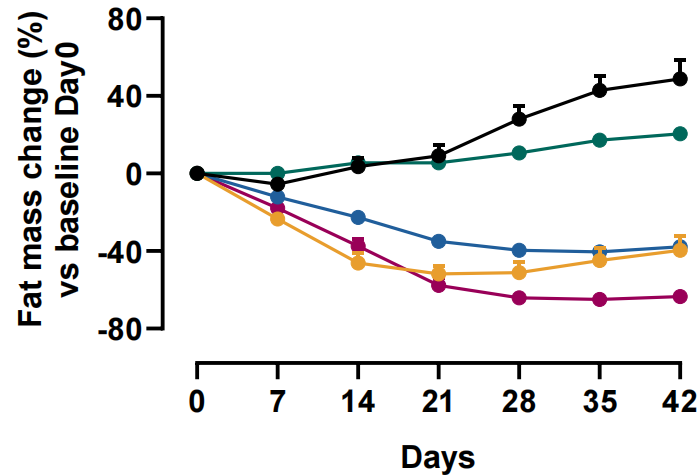
**ASC47 preserved total muscle mass(+5.8%) compared to a decline in total muscle mass of semaglutide (-9.3%).**
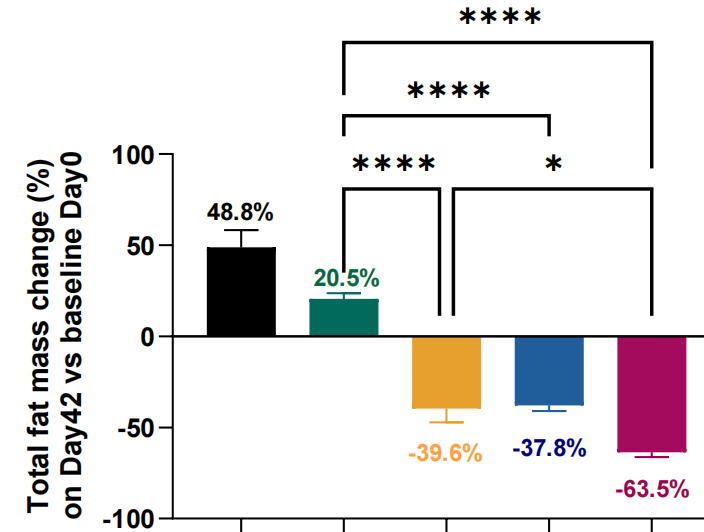
Note:
1. Body lean mass by MRI determined on Day42

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# Adipose-targeted ASC47 reduced significantly more fat than semaglutide



Non-obese mice, Vehicle, Q2W, SQ
DIO, Vehicle, Q2W, SQ
DIO, Semaglutide(30 nmol/kg), QD, SQ
DIO, ASC47(15 mg/kg), Q2W, SQ
DIO, ASC47(45 mg/kg), Q2W, SQ

Data were presented as Mean ± SEM, One way ANOVA followed by Tukey test by Prism GraphPad; N=10. * $p<0.05$, **** $p<0.0001$

**ASC47 (45 mg/kg) reduced total fat mass (-63.5%), statistically and significantly more than semaglutide (-39.6%)**
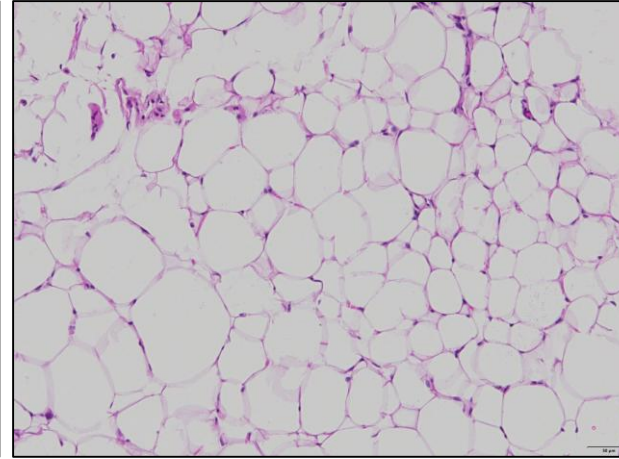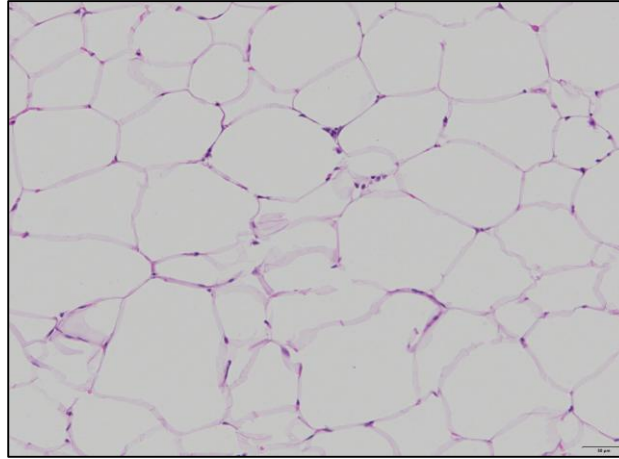
Note:
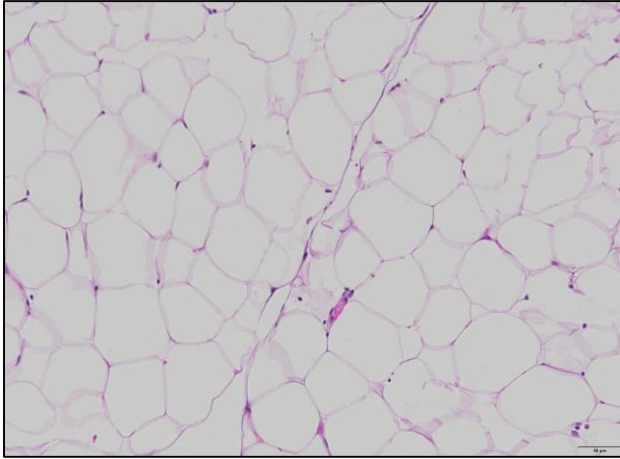1. Body fat mass by MRI determined on Day42
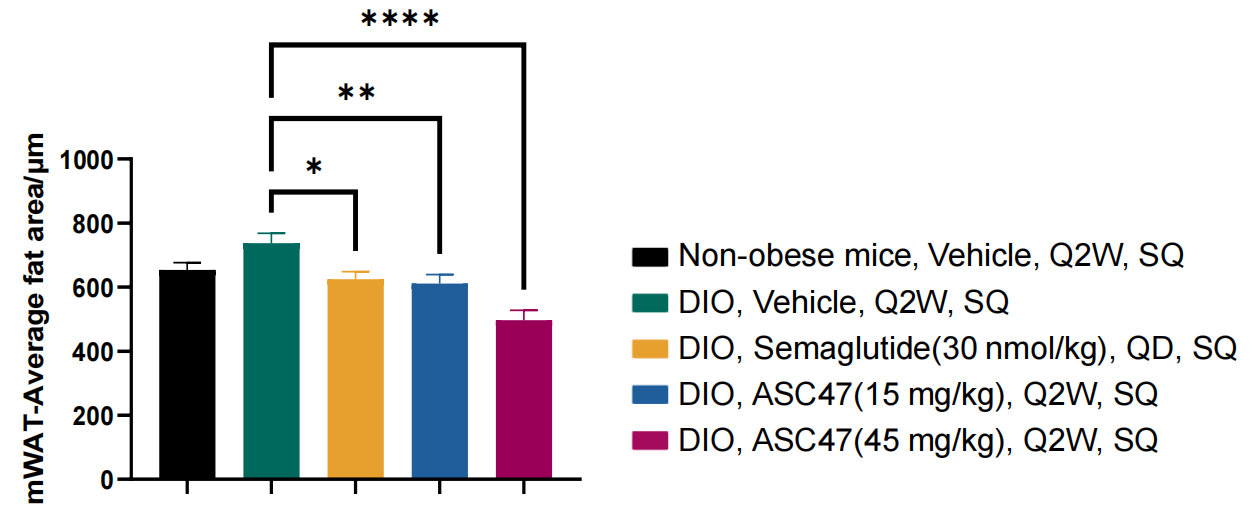
# Adipose-targeted ASC47 reduced adipose cell size



Non-obese

DIO

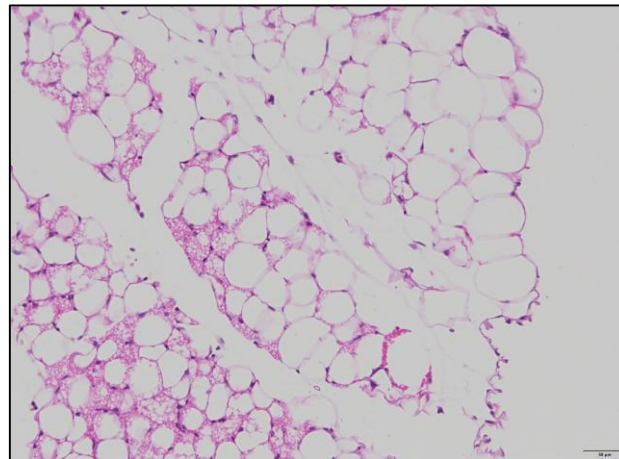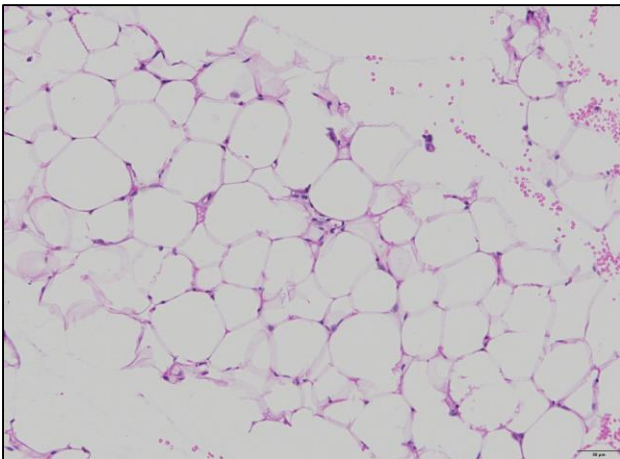Semaglutide  30nmol/kg

ASC47 15 mg/kg

ASC47 45 mg/kg

Legend:
- ■ Non-obese mice, Vehicle, Q2W, SQ
- ■ DIO, Vehicle, Q2W, SQ
- ■ DIO, Semaglutide(30 nmol/kg), QD, SQ
- ■ DIO, ASC47(15 mg/kg), Q2W, SQ
- ■ DIO, ASC47(45 mg/kg), Q2W, SQ

Note:
mWAT: mesenteric white adipose tissue

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# ASC47 reduced blood glucose and insulin resistance



Data were presented as Mean ± SEM, One way ANOVA followed by Tukey test by Prism GraphPad; N=10. **** *p*<0.0001

■ Non-obese mice, Vehicle, Q2W, SQ
■ DIO, Vehicle, Q2W, SQ
■ DIO, Semaglutide(30 nmol/kg), QD, SQ
■ DIO, ASC47(15 mg/kg), Q2W, SQ
■ DIO, ASC47(45 mg/kg), Q2W, SQ
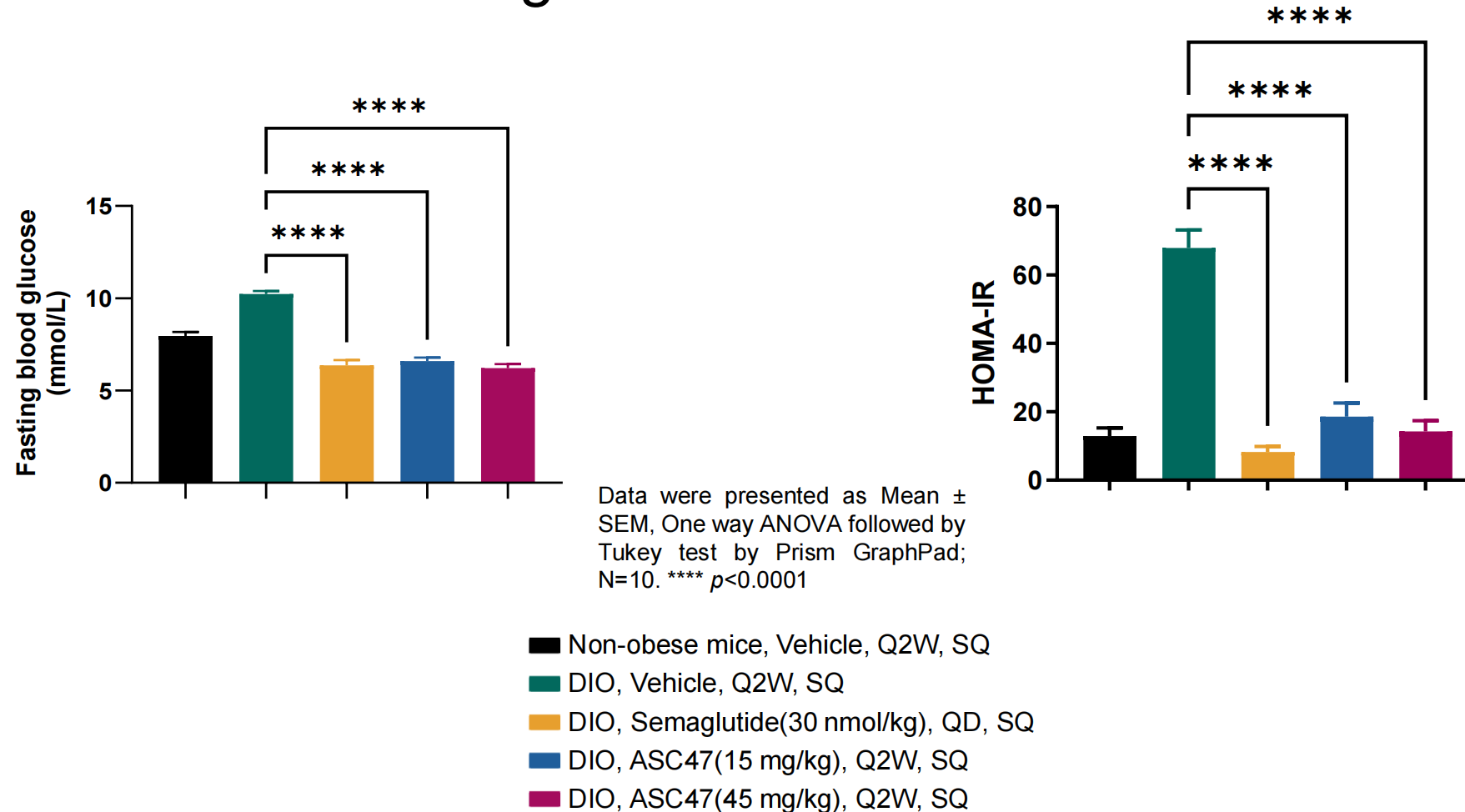
**Similar reductions were observed in fasting blood glucose and insulin resistance between ASC47 and semaglutide**

# ASC47 reduced more blood lipids than semaglutide



Non-obese mice, Vehicle, Q2W, SQ
DIO, Vehicle, Q2W, SQ
DIO, Semaglutide(30 nmol/kg), QD, SQ
DIO, ASC47(15 mg/kg), Q2W, SQ
DIO, ASC47(45 mg/kg), Q2W, SQ

Data were presented as Mean ± SEM, One way ANOVA followed by Tukey test by Prism GraphPad; N=10. **** $p<0.0001$
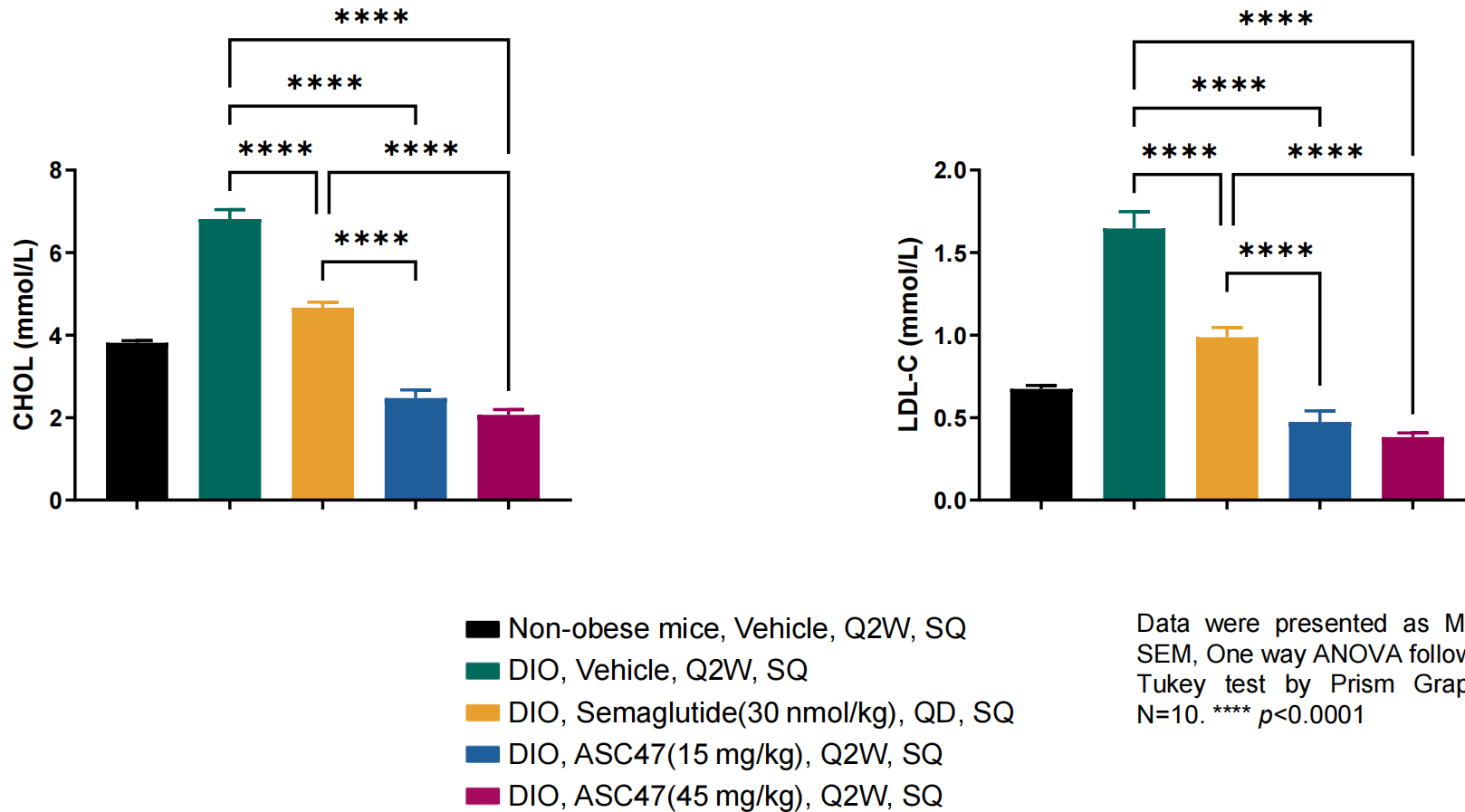
**Significant decreases of blood lipid were observed in ASC47-treated group compared with semaglutide-treated group.**

# ASC47 Summary

- **ASC47 is an adipose-targeted, ultra-long-acting and THRβ selective small molecule agonist.**

- **ASC47 demonstrates similar weight loss to semaglutide but preserves muscle in DIO mice.**

- **ASC47 is safe and well tolerated in Phase Ib study with healthy subjects and participants with obesity and demonstrates a half-life of up to 40 days, supporting further clinical evaluations.**
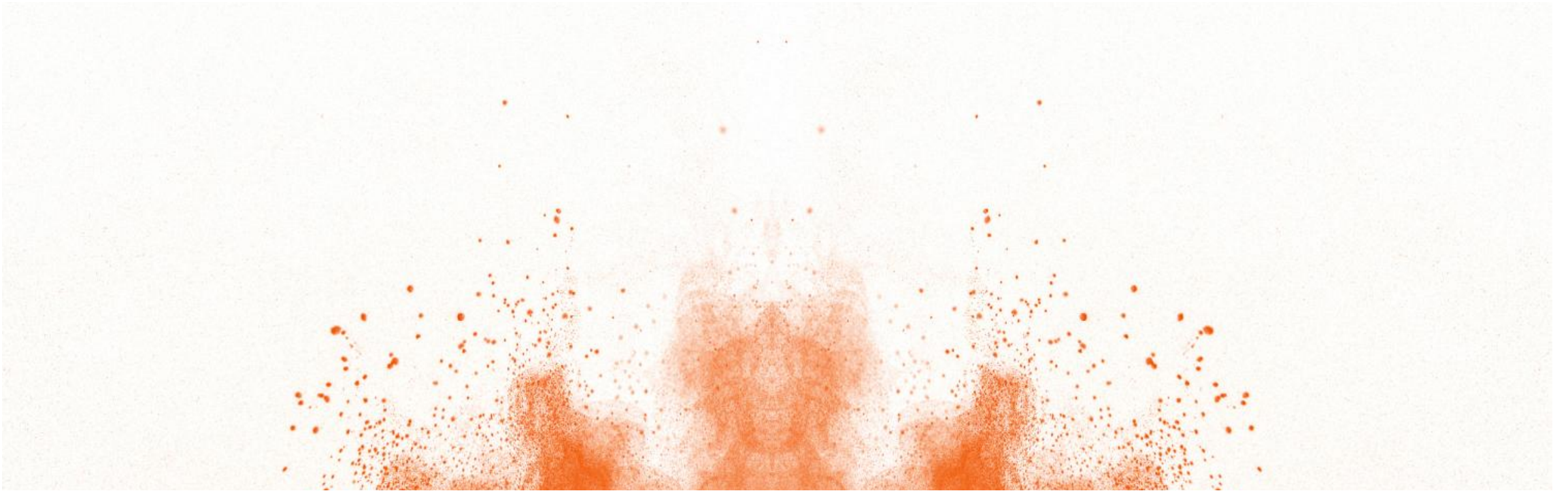
# Thanks

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