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

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Disclosure

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

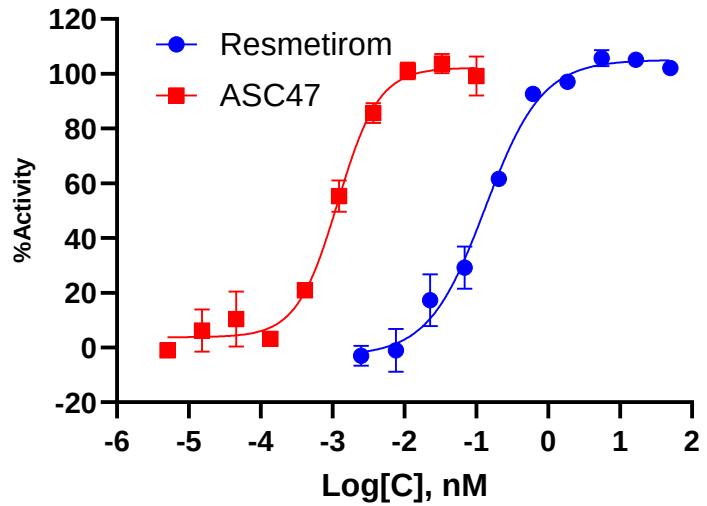
Overview of ASC47

- **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



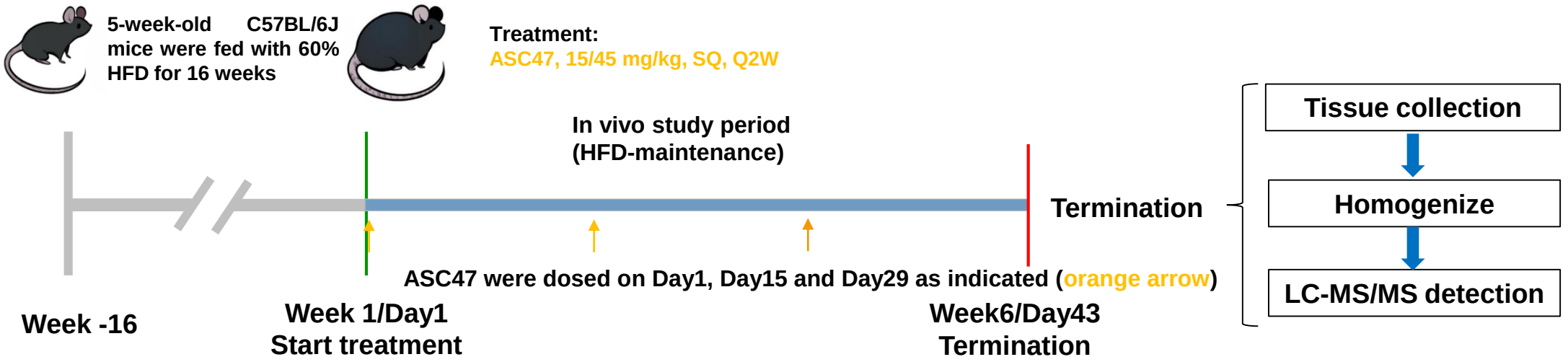
Compound ID	EC_{50} (μM)
Resmetirom	0.133
ASC47	0.001

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.

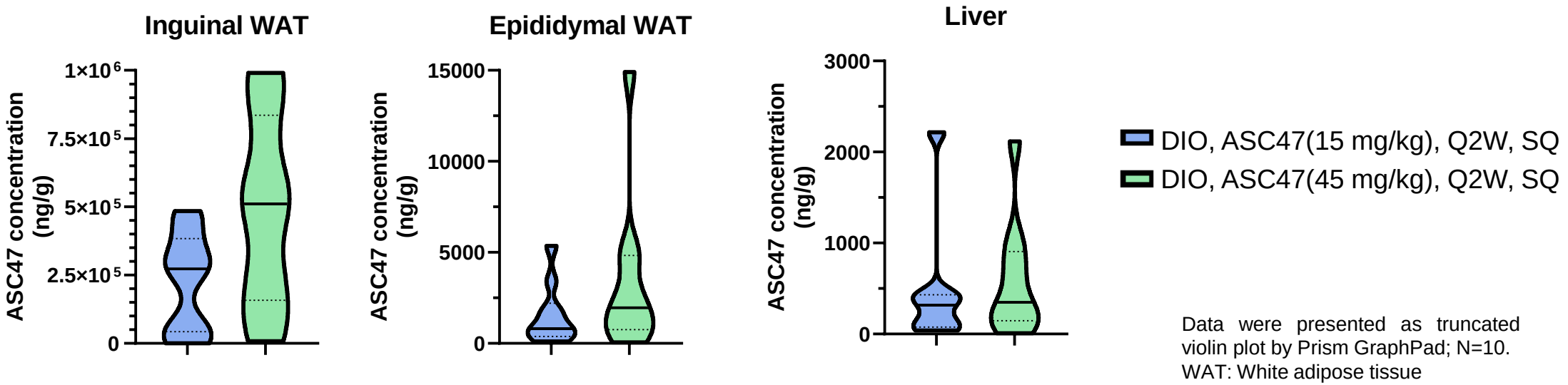
Study Design: ASC47 tissue distribution in DIO mice



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



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

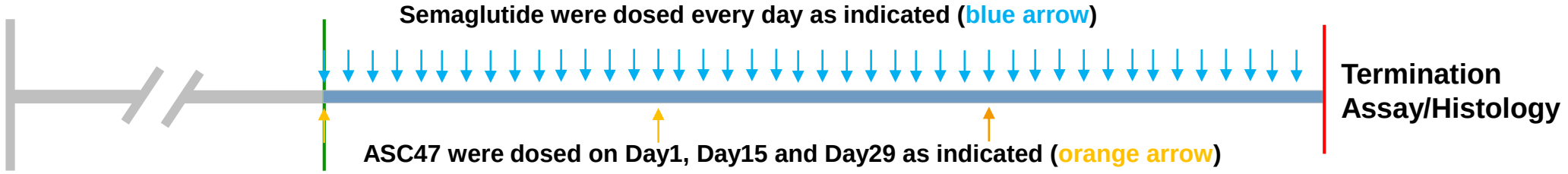
ASC47 tissue distribution ratio

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

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



Week -16

Week 1/Day1
Start treatment

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

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

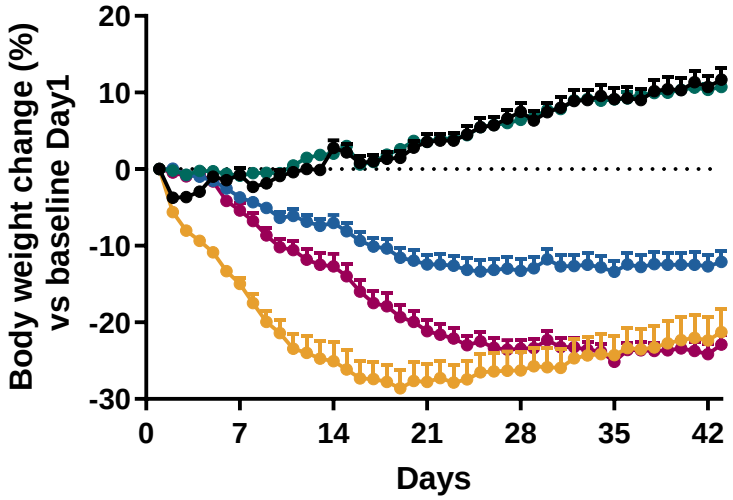
Week6/Day43
Endpoint

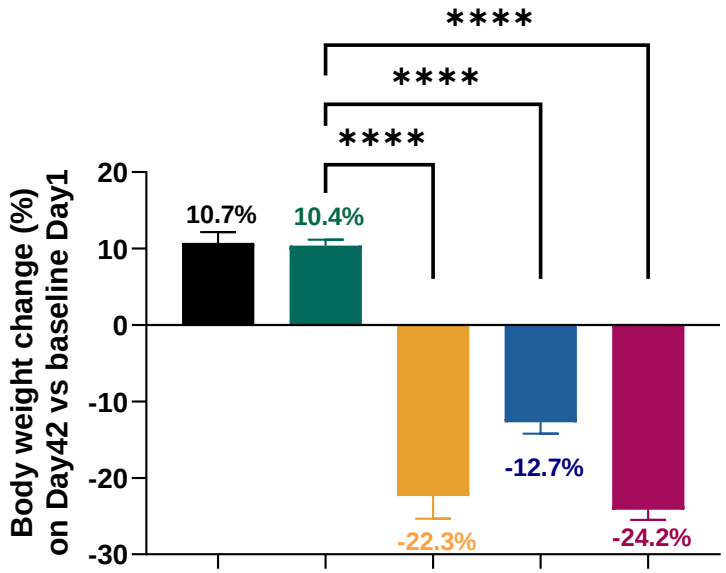
Assay:
+ Fasting blood glucose / HOMA-IR
+ Plasma CHOL/HDL-c/LDL-c
+ Liver TG/CHOL

Histology
+ WAT cell size

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

ASC47 Q2W produced similar weight loss to Sema QD





- 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

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

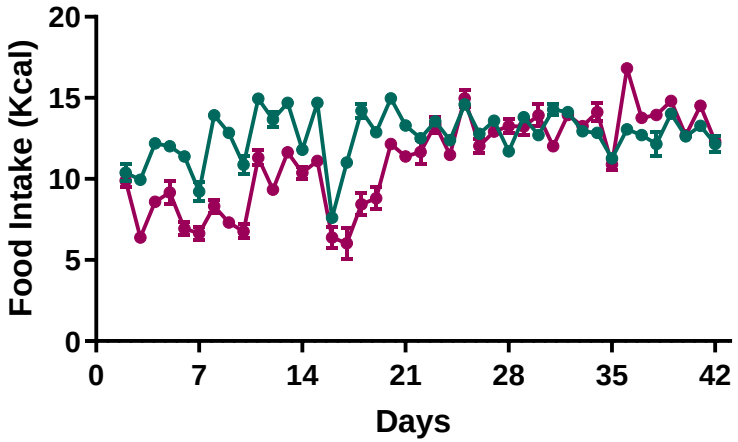
Total body weight reduction was similar between semaglutide (30nmol/kg, QD) and ASC47 (45mg/kg, Q2W). However, speed of weight loss by ASC47 was lower than semaglutide.

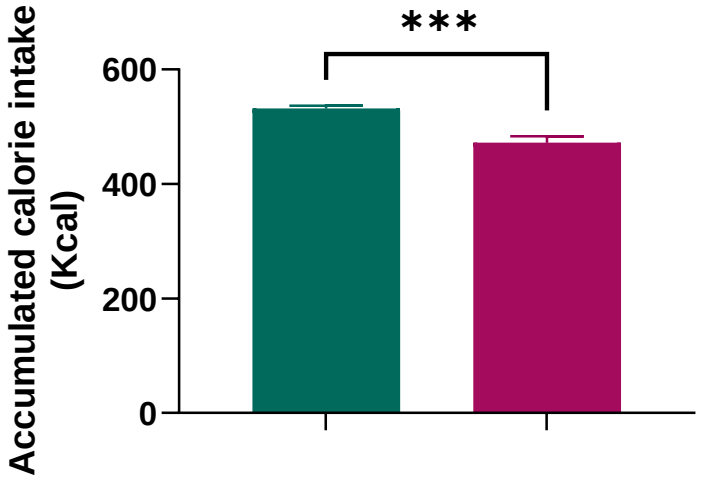
ASC47 to treat obesity: Two major mechanisms of action (MOA)

- **Induce satiety and decrease caloric intake**

- **Preserve muscle and reduce fat**

ASC47 induced satiety and decreased caloric intake in DIO mice





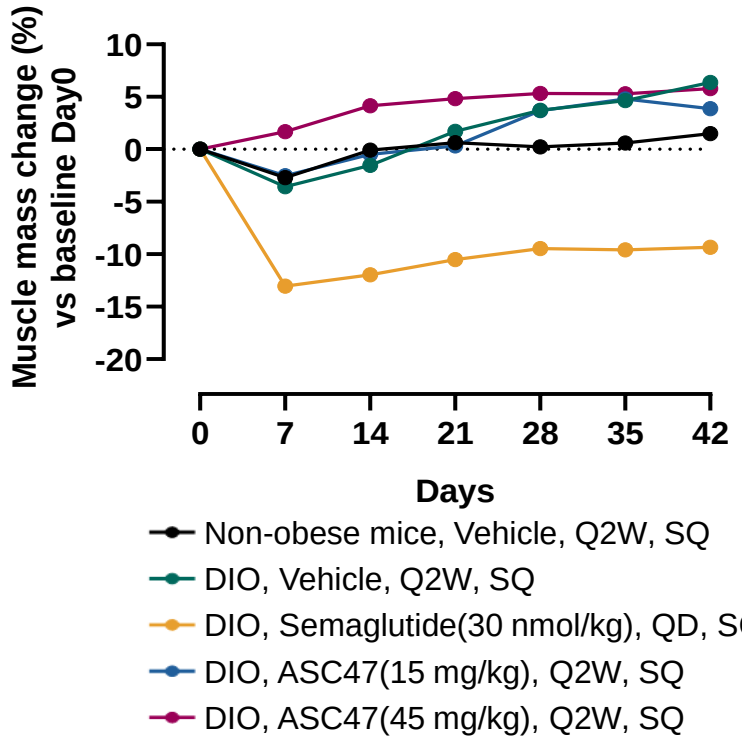
DIO, Vehicle, Q2W, SQ
DIO, ASC47(45 mg/kg), Q2W, SQ

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



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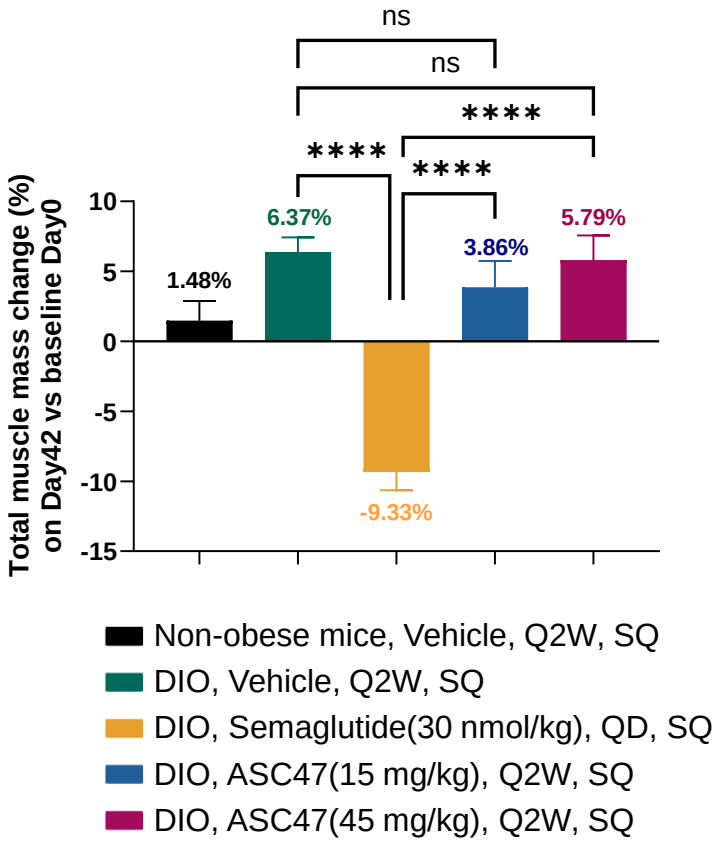
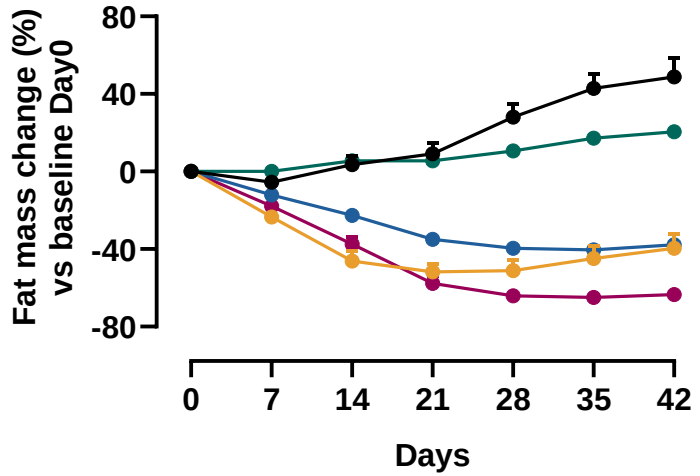
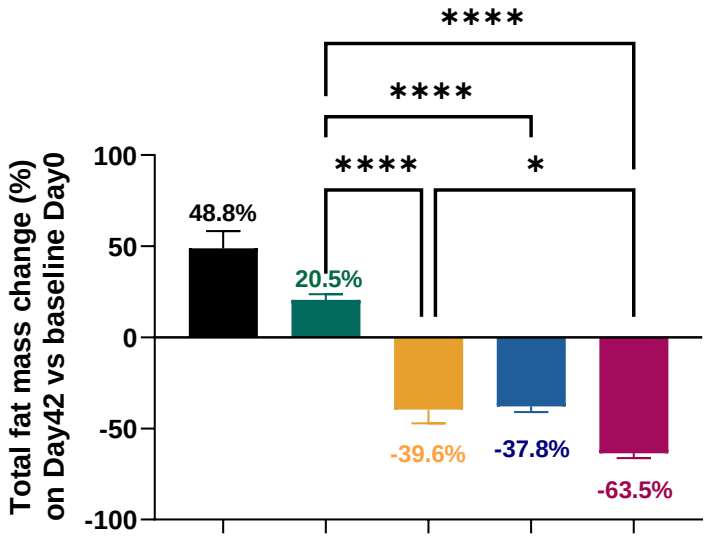


ASC47 preserved total muscle mass(+5.8%) compared to a decline in total muscle mass of semaglutide (-9.3%).

Note:
1. Body lean mass by MRI determined on Day42

Adipose-targeted ASC47 reduced significantly more fat than semaglutide





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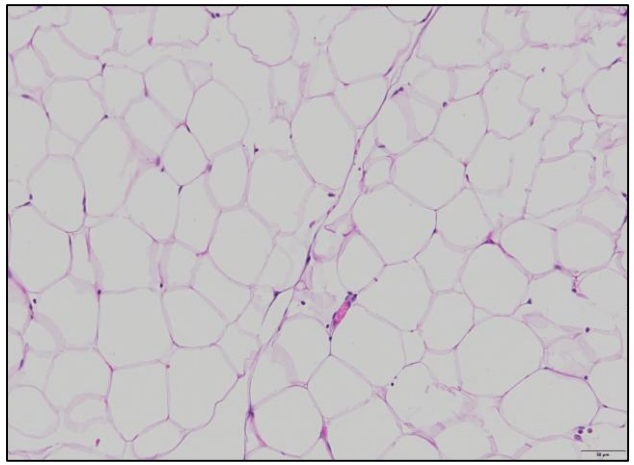
Data were presented as Mean ± SEM, One way ANOVA followed by Tukey test by Prism GraphPad; N=10. * $p<0.05$, **** $p<0.0001$

ASC47 (45 mg/kg) reduced total fat mass (-63.5%), statistically and significantly more than semaglutide (-39.6%)

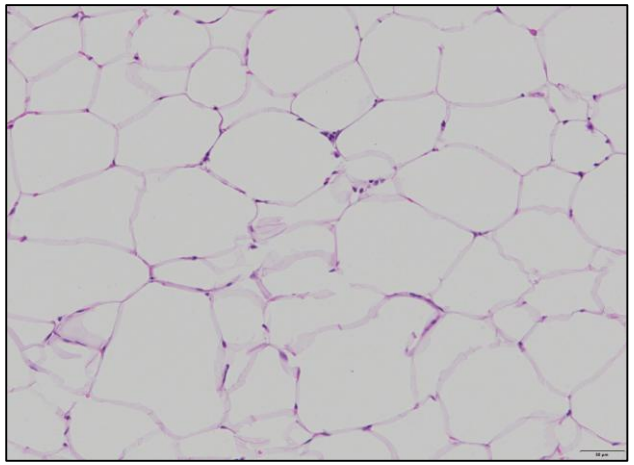
Note:
1. Body fat mass by MRI determined on Day42

Adipose-targeted ASC47 reduced adipose cell size

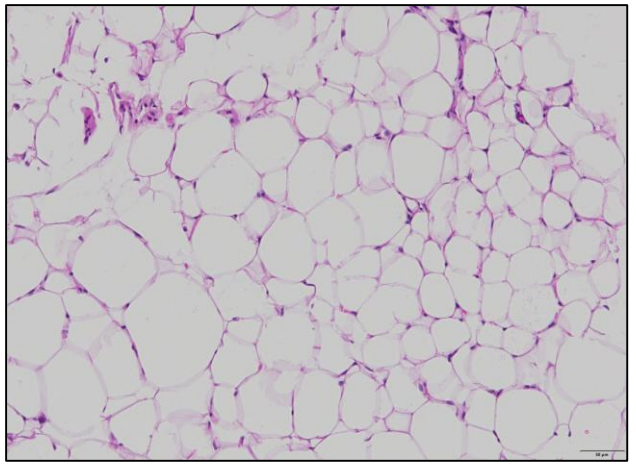
Non-obese



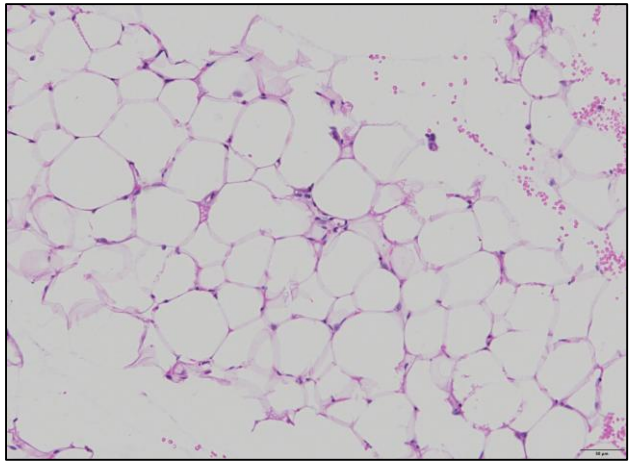
DIO



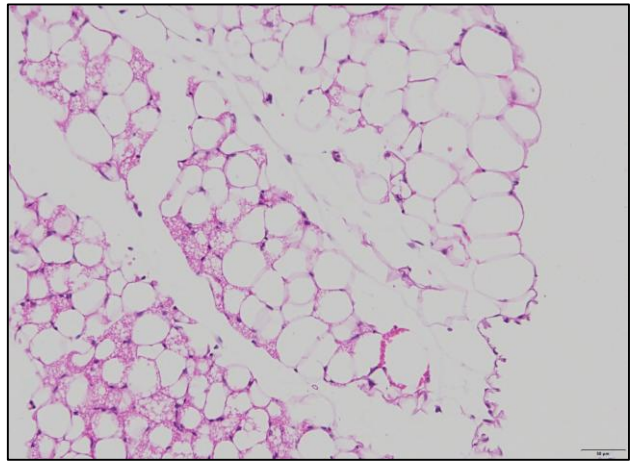
Semaglutide 30nmol/kg

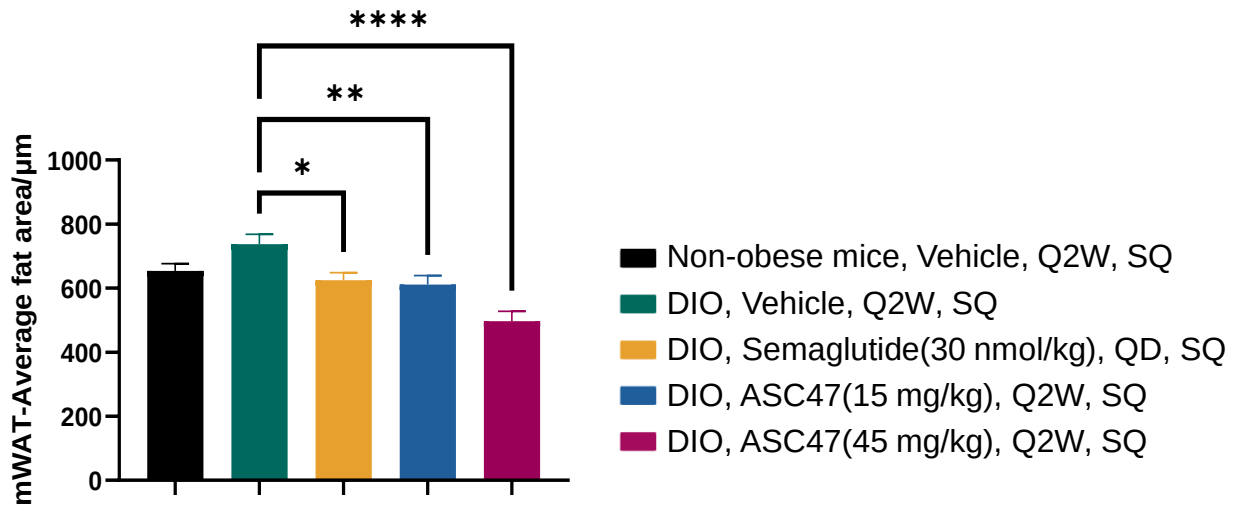


ASC47 15 mg/kg



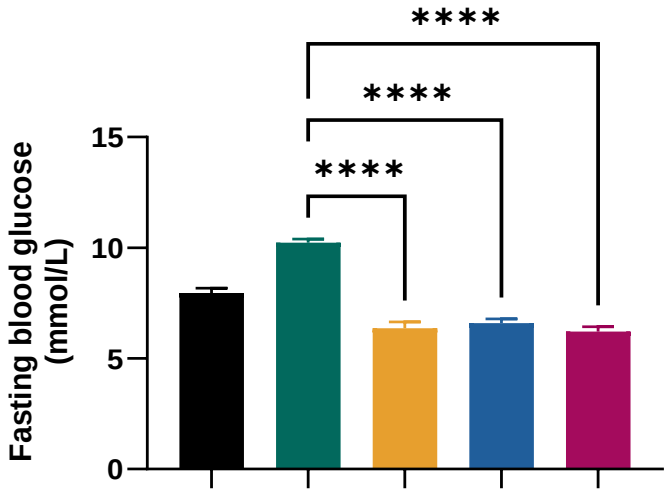
ASC47 45 mg/kg

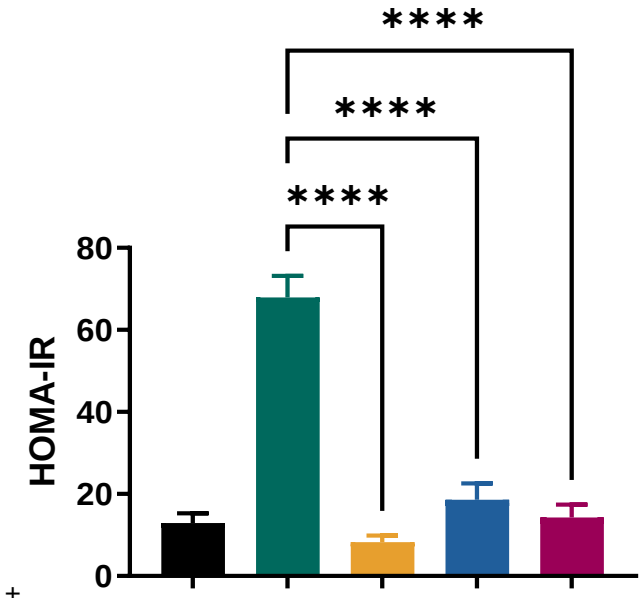




Note:
mWAT: mesenteric white adipose tissue

ASC47 reduced blood glucose and insulin resistance





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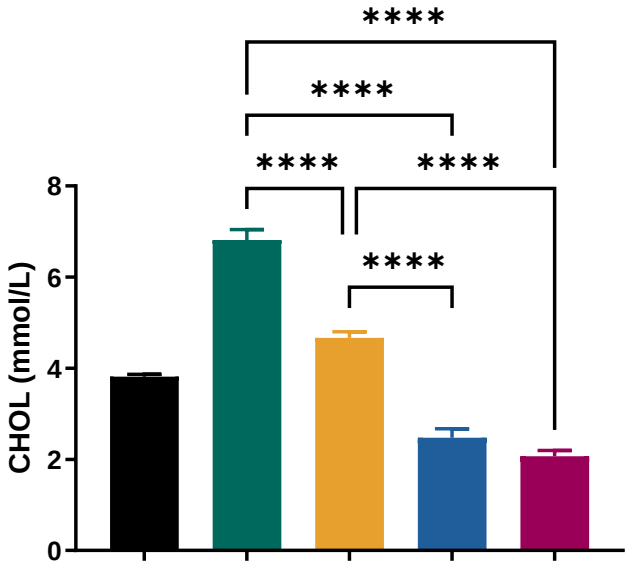
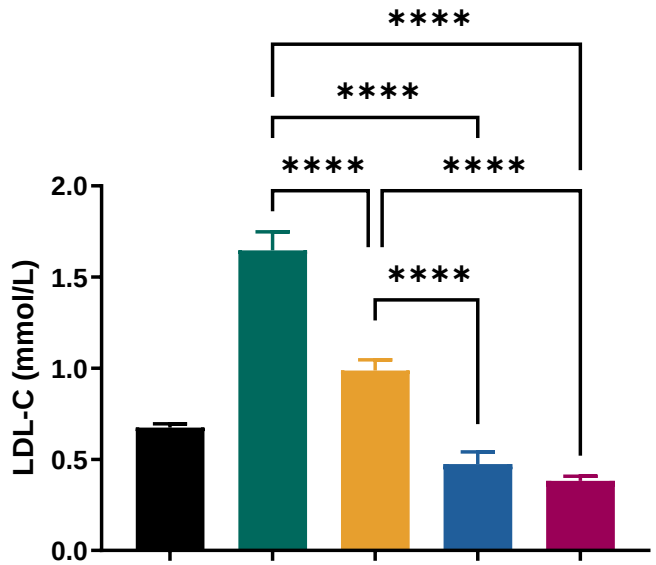
- DIO, ASC47(45 mg/kg), Q2W, SQ

Similar reductions were observed in fasting blood glucose and insulin resistance between ASC47 and semaglutide

ASC47 reduced more blood lipids than semaglutide





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

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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