The novel GIP, GLP-1, and Glucagon Triple Receptor Agonist LY3437943 Exhibits Robust Efficacy in Preclinical Models of Obesity and Diabetes

Tamer Coskun, Julie S. Moyers, William Roell, Libbey O'Farrell, Ajit Regmi, Xiaoping Ruan, Aaron D. Showalter, Kyle W. Sloop, David B. Wainscott, Francis Willard, James Ficorilli, Over Cabrera, Shweta Urva, Fariba Norouziyan Cooper, Lili Guo, Jorge Alsina-Fernandez, Hongchang Qu

Eli Lilly and Company, Indianapolis, USA

American Diabetes Association – 81st Annual Scientific Sessions; Virtual; 25-29 June 2021

Disclosures

All authors are employees and shareholders of Eli Lilly and Company.

Scan or click the QR code, or use this URL:
https://lillyscience.lilly.com/congress/ada2021
for a list of all Lilly content presented at the congress.

BACKGROUND AND OBJECTIVE

Background

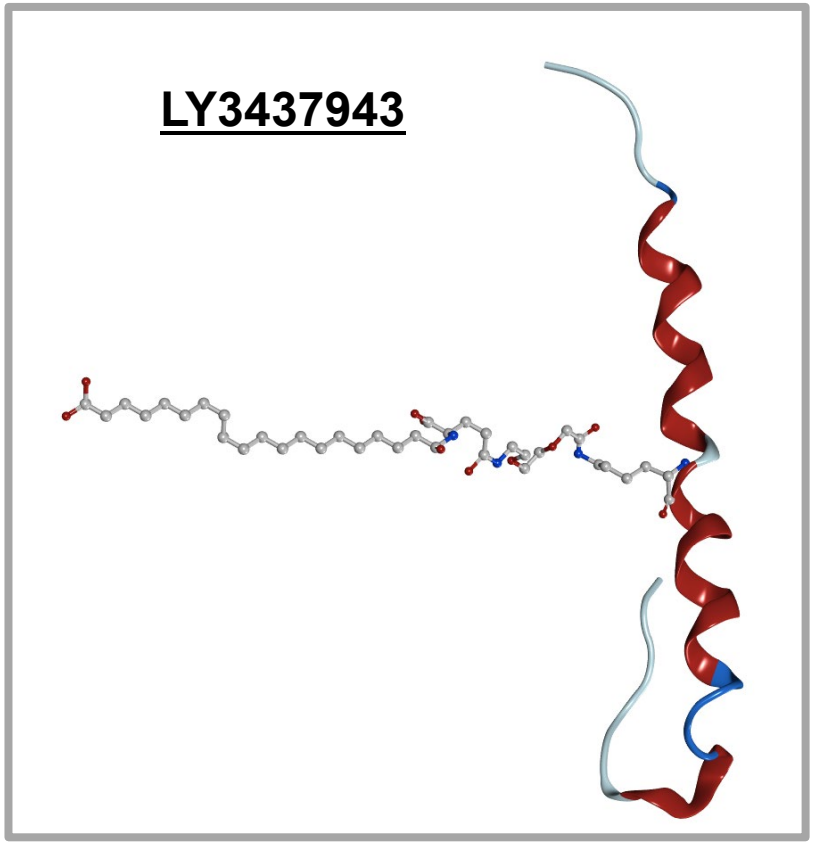
- The dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, tirzepatide, demonstrates superior glucose lowering and body weight loss compared to selective GLP-1RAs[1]
- Glucagon (GCG)[2] or dual GLP-1/GCG receptor agonists[3] increase energy expenditure and improve liver health[4]

LY3437943

- Novel single peptide derived from a GIP peptide backbone with triple agonist activity on GIPR, GLP-1R and GCGR
- Activity ratio between GIPR and GLP-1R is alike tirzepatide
- GCGR activity is alike native GCG

Objective

- To characterize LY3437943 *in vitro* and *in vivo*



1. Frias et al. Lancet 2018;392(10160):2180-93.
2. Salem et al. Diabetes Obes Metab. 2016; 18(1):72-81
3. Henderson et al. Diabetes Obes Metab. 2016;18(12):1176-1190
4. Boland et al. Nat Metab. 2020;2(5):413-431

GCGR=glucagon receptor; GIPR=glucose-dependent insulinotropic polypeptide; GLP-1R=glucagon-like peptide-1 receptor; GLP-1RAs=glucagon-like peptide-1 receptor agonists

LY3437943 Activates Human (h) GIP, GLP-1 and GCG Receptors *In Vitro*

Functional cAMP Potency (EC_{50}) for Compounds Incubated at 37°C in the Presence of 0.1% Bovine Casein

	hGIP-R EC_{50}, nM (SE, n)	hGIP-R EC_{50} ratio[2]	hGLP-1R EC_{50}, nM (SE, n)	hGLP-1R EC_{50} ratio[2]	hGCGR EC_{50}, nM (SE, n)	hGCGR EC_{50} ratio[2]
LY3437943	0.0825 (0.0114, 8)	0.14	0.490 (0.089, 7)	1.7	4.59 (0.75, 7)	2.5
Native Ligand[1]	0.574 (0.099, 22)		0.285 (0.036, 25)		1.87 (0.24, 37)	

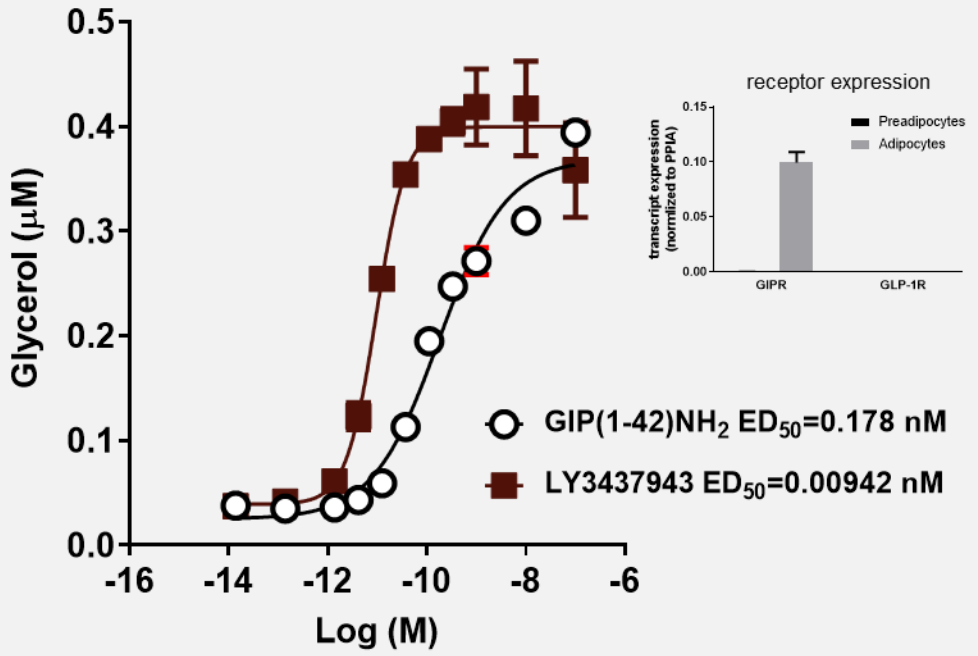
- The unbalanced activity profile of LY3437943 for human GIPR and GLP-1R is similar to tirzepatide

Methods: Functional cAMP data is generated in the presence of bovine casein (without serum albumin), using HEK-293 clonal cell lines having a low expression density of human GIPR, GLP-1R or human GCGR.

[1]EC_{50} determination of human GLP-1(7-36)NH_2 at human GLP-1R, human GIP(1-42)NH_2 at human GIPR or human glucagon at human GCGR.
[2]EC_{50} ratio is calculated as the potency value of LY3437943 divided by the potency value of native ligand.

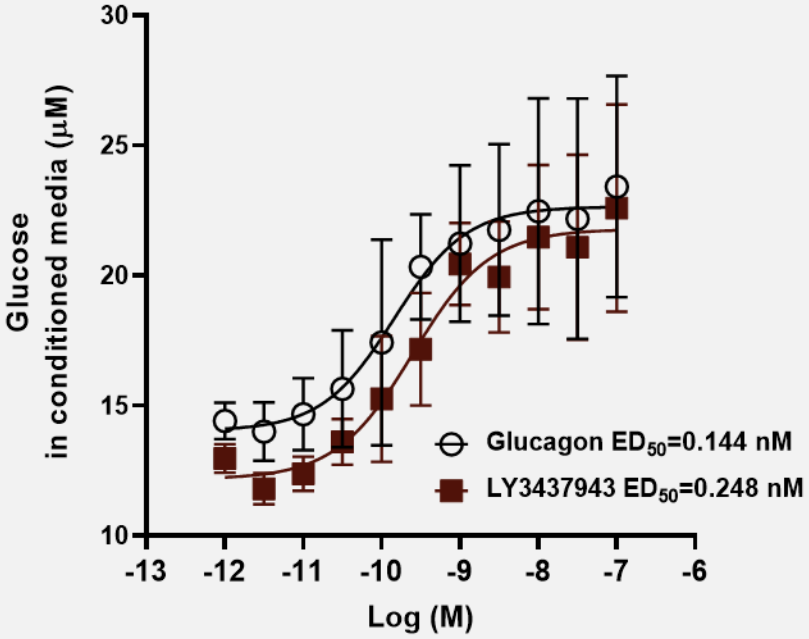
LY3437943 Regulates Human Adipocyte Lipolysis By GIPR and Human Hepatocyte Glucose Output By GCGR

Differentiated Human Adipocytes



- Human adipocytes express GIPR[1] but not GLP-1R
- LY3437943 is 19 times more potent than GIP in stimulating lipolysis in human adipocytes

iPSC-Derived Human Hepatocytes

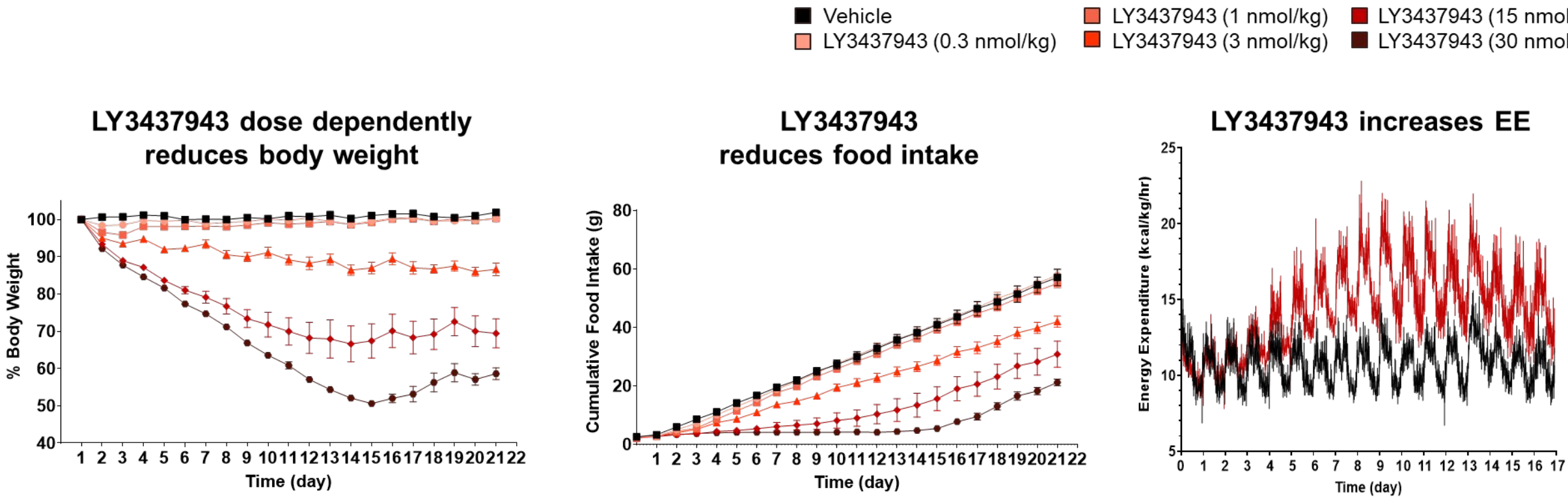


- Induced pluripotent stem cell (iPSC) derived human hepatocytes only express GCGR
- LY3437943 is 0.6 times less potent than glucagon in stimulation of glucose output in human hepatocytes

Methods: Differentiated Human Adipocytes: Isolated and cultured human preadipocytes (ZenBio, SP-2006-1, lot L020206) are differentiated into mature adipocytes. Glycerol content is measured in conditioned media after incubation with test articles
iPSC-Derived Human Hepatocytes: Hepatocyte glucose output is measured in cultured human induced pluripotent stem cell-derived hepatocytes

1. Ceperuelo-Mallafre et al, JECM. 2014; 99(5):E908-19

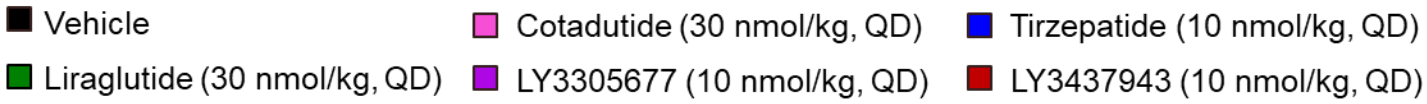
LY3437943 Causes Body Weight Loss by Reducing Food Intake and Increasing Energy Expenditure (EE) in Diet-Induced Obese (DIO) Mice

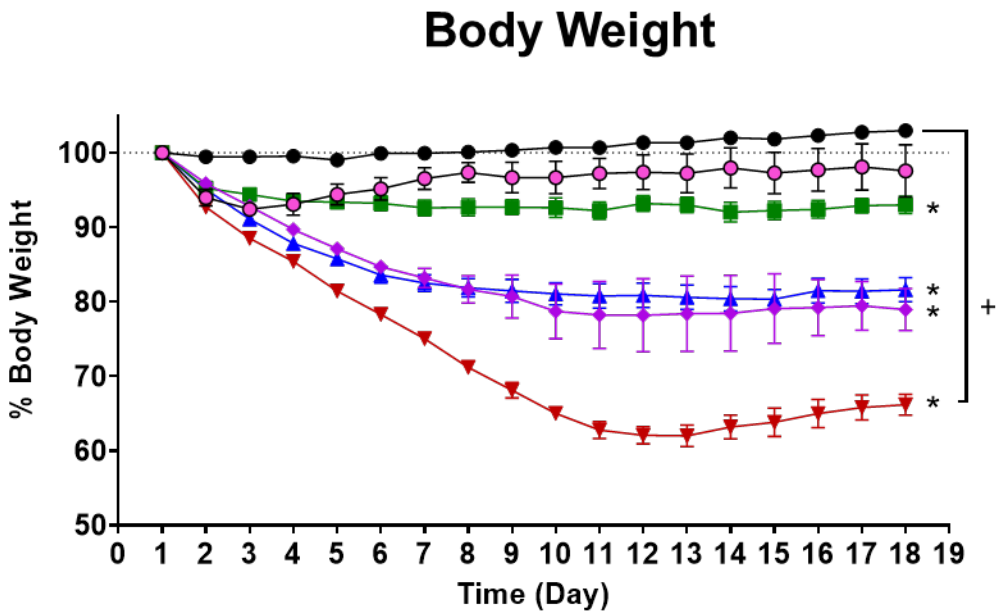


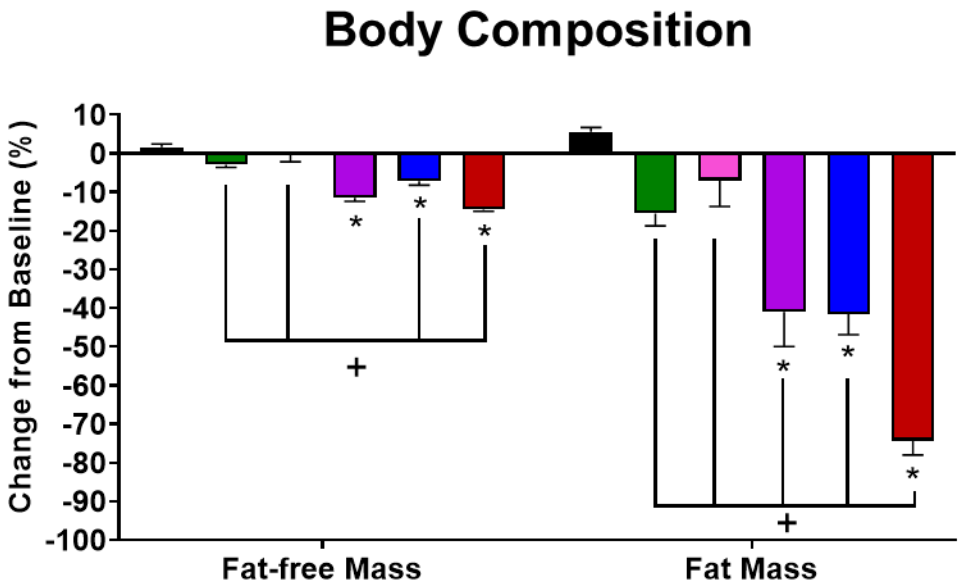
- LY3437943 causes increase in energy expenditure with profound reduction in food intake
- ED_{50} for LY3437943 on percent weight loss in DIO mice is calculated as 4.73 nMol/kg (95% CI 3.82-5.86)

Methods: Male DIO C57/Bl6 mice 24 to 25 weeks old are maintained on a calorie-rich diet. Treatments are administered subcutaneously on Days 1, 4, 7, 10, 13, 16 and 19. Body weight and food intake are measured daily throughout the study. Separate animal cohorts are placed in indirect calorimetry chambers maintained at 24°C and energy expenditure is assessed.

LY3437943 Causes Significantly More Weight Loss Compared to Selective and Dual GLP-1 Receptor Agonists





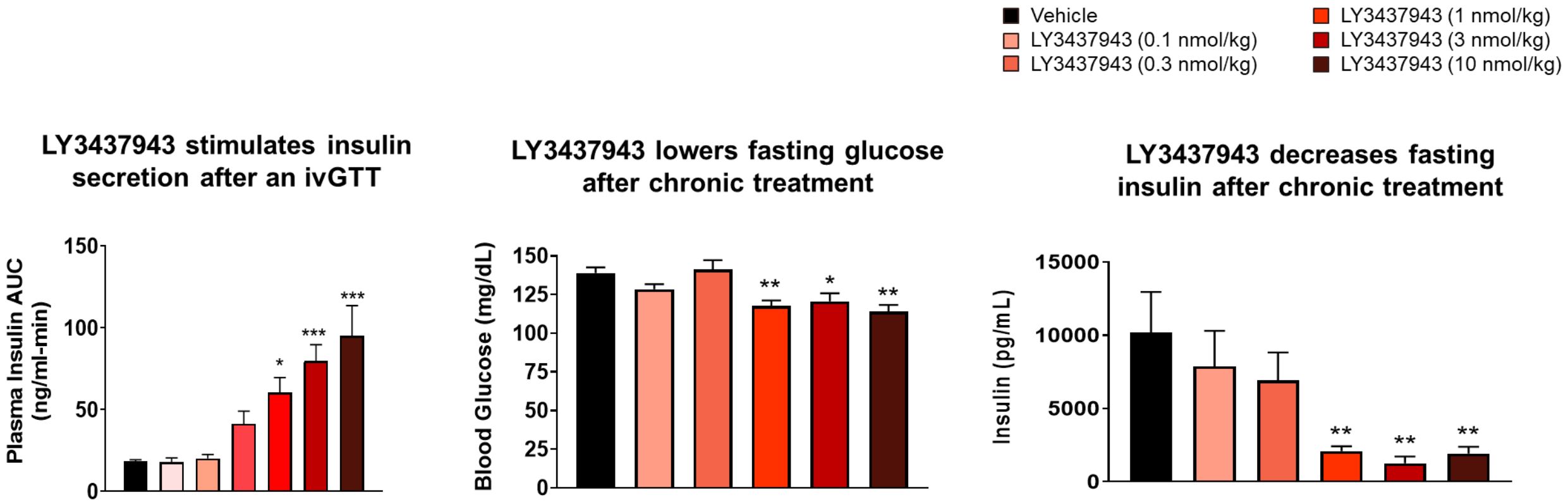


- LY3437943 shows superior weight loss compared to selective GLP-1 RA and dual agonists (e.g. Cotadutide or LY3305677 [dual GLP-1R/GCGR agonist] or tirzepatide [dual GIPR/GLP-1R agonist])
- The weight loss observed is mainly driven by fat mass loss (~80%)

*$p<0.05$ vs Vehicle and +$p<0.05$ vs LY3437943

Methods: DIO male C57/Bl6 mice 24 to 25 weeks old, maintained on a calorie rich diet are placed in indirect calorimetry chambers maintained at 24°C throughout the study. Daily treatments are administered and body weight and food intake are measured. Body composition is measured by quantitative magnetic resonance before starting the treatments and at the end.

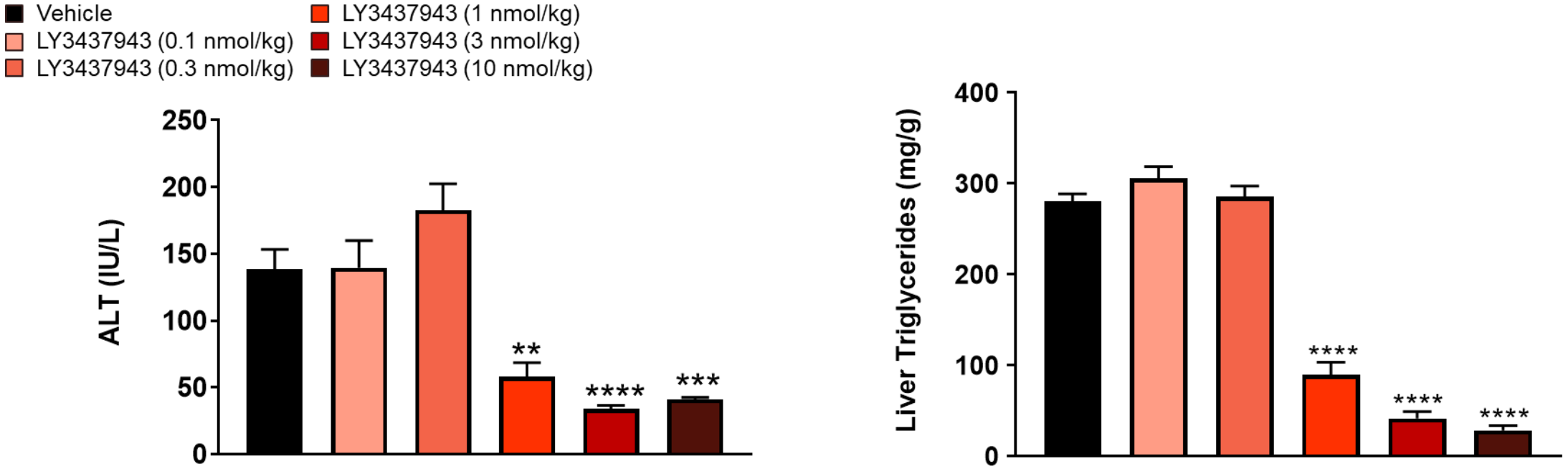
LY3437943 Stimulates Glucose-Dependent Insulin Secretion and Improves Insulin Sensitivity



- LY3437943 exerts its glucose lowering activity by augmenting the glucose-dependent insulin secretion, here in a rat ivGTT model
- LY3437943 lowers fasting glucose and insulin in obese mice, indicating improvement in insulin sensitivity

*p<0.05, **p<0.01 and ***p<0.001 vs vehicle; One-way ANOVA, Dunnett's

LY3437943 Shows A Robust Effect in Lowering Liver Fat and Decreases Markers of Liver Injury in Obese Mice



- The selective GLP-1 receptor agonist semaglutide has shown potential for improving liver health. The effects of semaglutide on the liver are attributed to its ability to decrease body weight[1]
- GCGR agonism directly engages the liver and is has been shown to reduce liver fat via increased beta oxidation and reduced de novo lipogenesis[2]
- The profound effect of LY3437943 on liver fat lowering may be a combination of direct effects on the liver (via GCGR) and indirect effects due to weight loss.

1. Newsome et al. N Engl J Med. 2021;384(12):1113-24.
2. Galsgaard et al. Front in Phys. 2019; 10:413

**p<0.01, ***p<0.001, ****p<0.0001 vs Vehicle; One-Way ANOVA, Dunnett's. GCGR=glucagon receptor; GLP-1R=glucagon-like peptide-1 receptor; ALT=alanine aminotransferase

SUMMARY AND CONCLUSION

- LY3437943 is a multifunctional agonist that activates GIP, GLP-1 and glucagon (GCG) receptors
  - LY3437943 potently activates all three receptors with a potency balance favoring GIPR (1.7- and 2.5-fold less potent at the GLP-1R and GCGR, respectively, but 7-fold more potent at the GIPR; all potencies in relation to the native ligands) in cAMP assays using recombinant cell lines expressing the individual receptors
  - LY3437943 induces lipolysis in differentiated human adipocytes and increases glucose output in iPSC-derived human hepatocytes, consistent with its actions on GIPR and GCGR, respectively
- LY3437943 acutely enhances glucose dependent insulin secretion in rats, demonstrated by ivGTT.
- LY3437943 decreases fasting glucose and insulin, contributing to improvement of insulin sensitivity in obese mice
- LY3437943 reduces food intake and increases energy expenditure resulting in a body weight loss superior to liraglutide, the dual GLP-1/GCG receptor agonists cotadutide and LY3305677, and the dual GIP/GLP-1 receptor agonist tirzepatide in obese mice
- LY3437943 decreases liver triglycerides and improves biomarkers of liver health in obese mice

CONCLUSION: ***LY3437943 is a novel triple agonist at the GIPR, GLP-1R, and GCGR, having differentiated efficacy on body weight and liver health.***

cAMP=cyclic AMP; GCGR=glucagon receptor; GIPR=glucose-dependent insulinotropic polypeptide; GLP-1R=glucagon-like peptide-1 receptor; iPCS=induced pluripotent stem cells; ivGTT=intravenous glucose tolerance test