58th European Association for the Study of Diabetes (EASD) Annual Meeting Short Oral Discussion Event E (572)

A novel oral cannabinoid receptor-1 (CB-1) inverse agonist induces additive weight loss and improves metabolic biomarkers in DIO mice in combination with semaglutide or tirzepatide

Marshall Morningstar, Suzie Ferreira, Andrew Kolodziej, Tracy Blumen, Zhuang Jin, Hongfeng Deng, Barbara White, Rachael Brake

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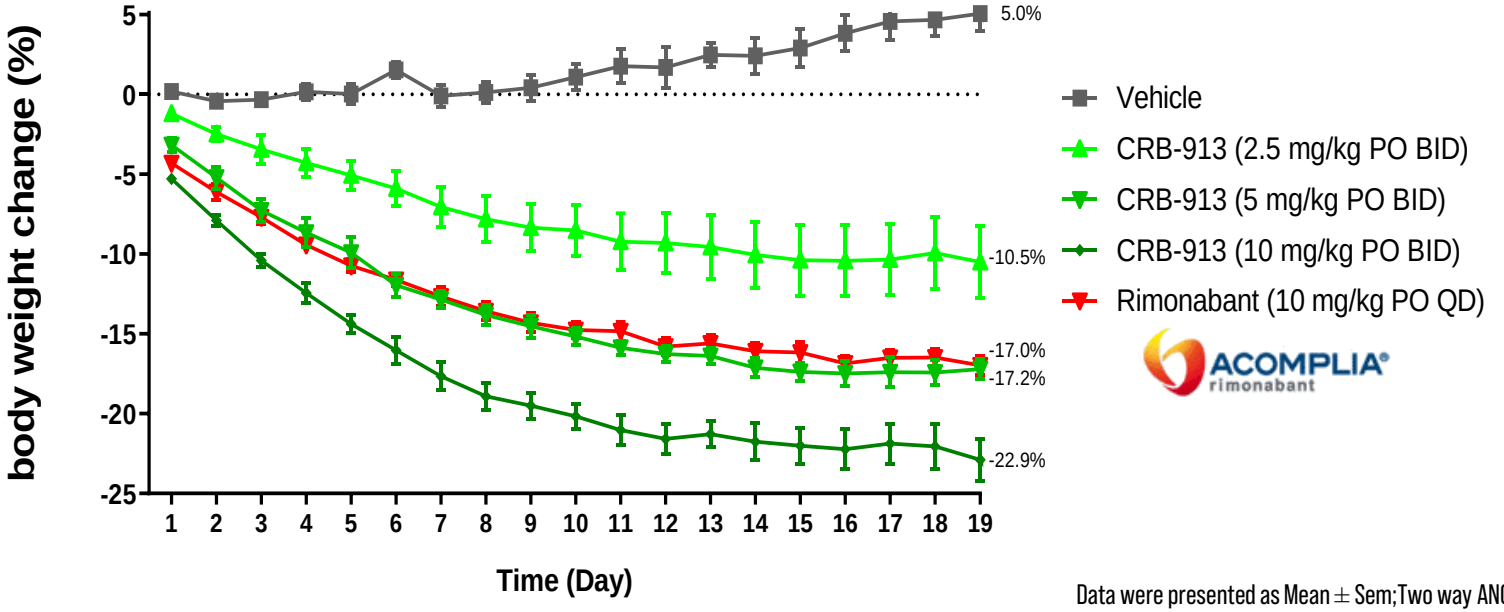
Overview

- CB1 is a clinically validated target in obesity
- CRB-913 is novel, oral CB1 inverse agonist
- Additive efficacy in combination with incretins
- CRB-913 is highly differentiated from 1st gen CB1 drugs (e.g., rimonabant)
- Progressing to Phase 1 enabling toxicology studies

Monotherapy (DIO Mouse Model)

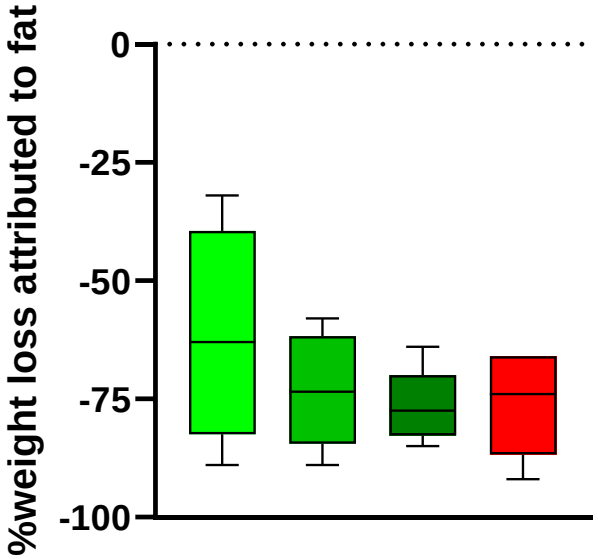
Percent (%) change of body weight



All cohorts P < 0.001 compared with vehicle

Data were presented as Mean ± Sem;Two way ANOVA followed by Dunnett test by Prism GraphPad; n=6.
*P<0.05,****P<0.0001 vs Vehicle

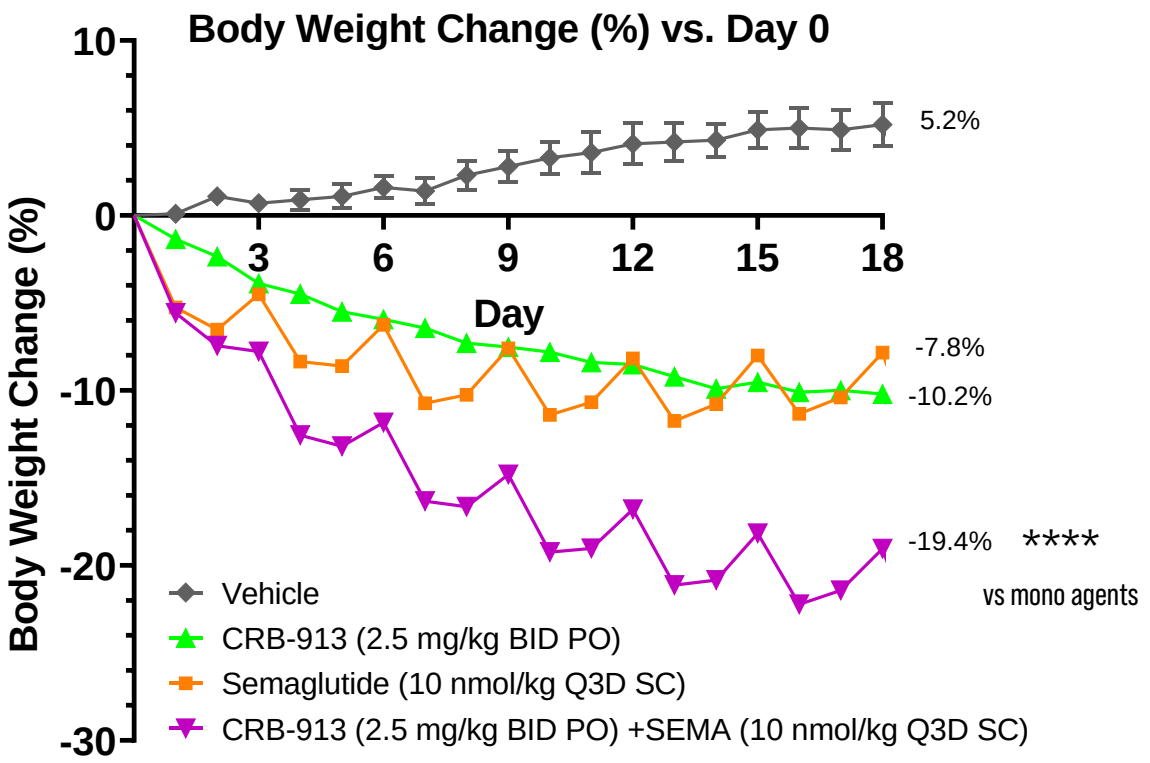
Decreased fat content



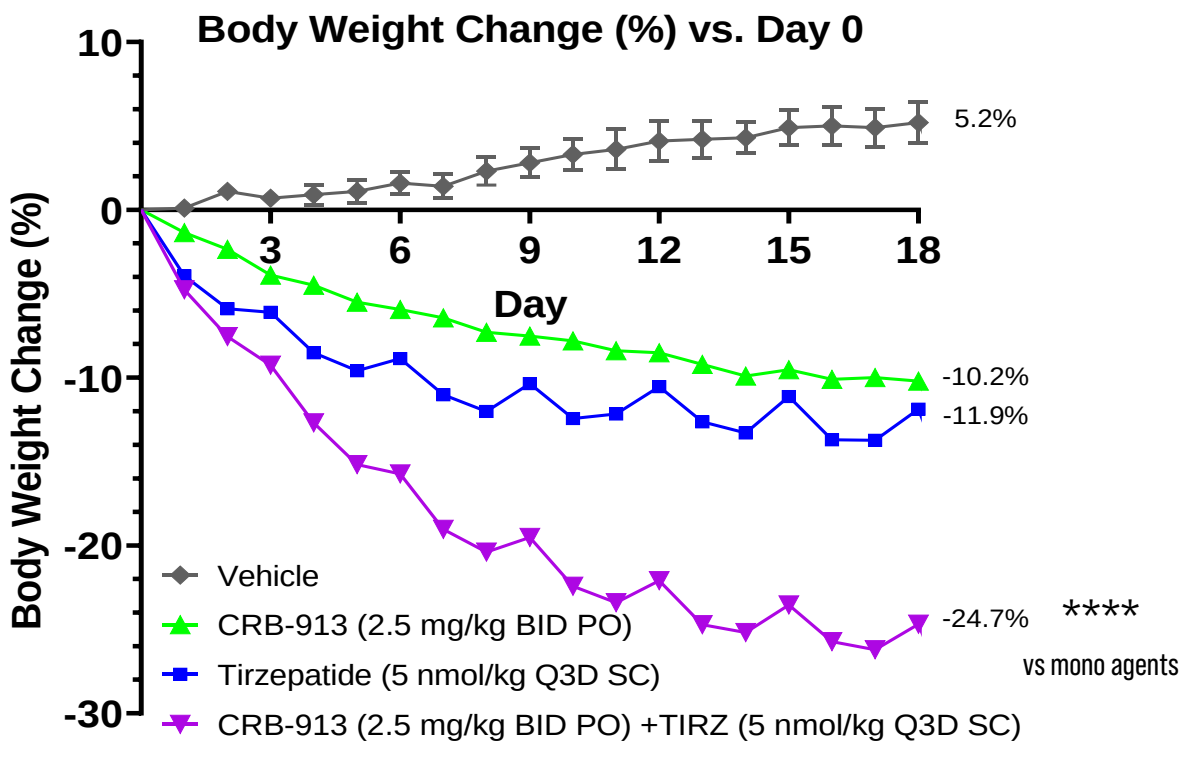
- DIO mouse model with C57BL6/J mice (n=10) fed a continuous high fat diet for 22 weeks prior
- Body fat by MRI determined on Day 20 after 5 h fasting and 2 h post final dose

Combination with liraglutide, semaglutide & tirzepatide

semaglutide



tirzepatide



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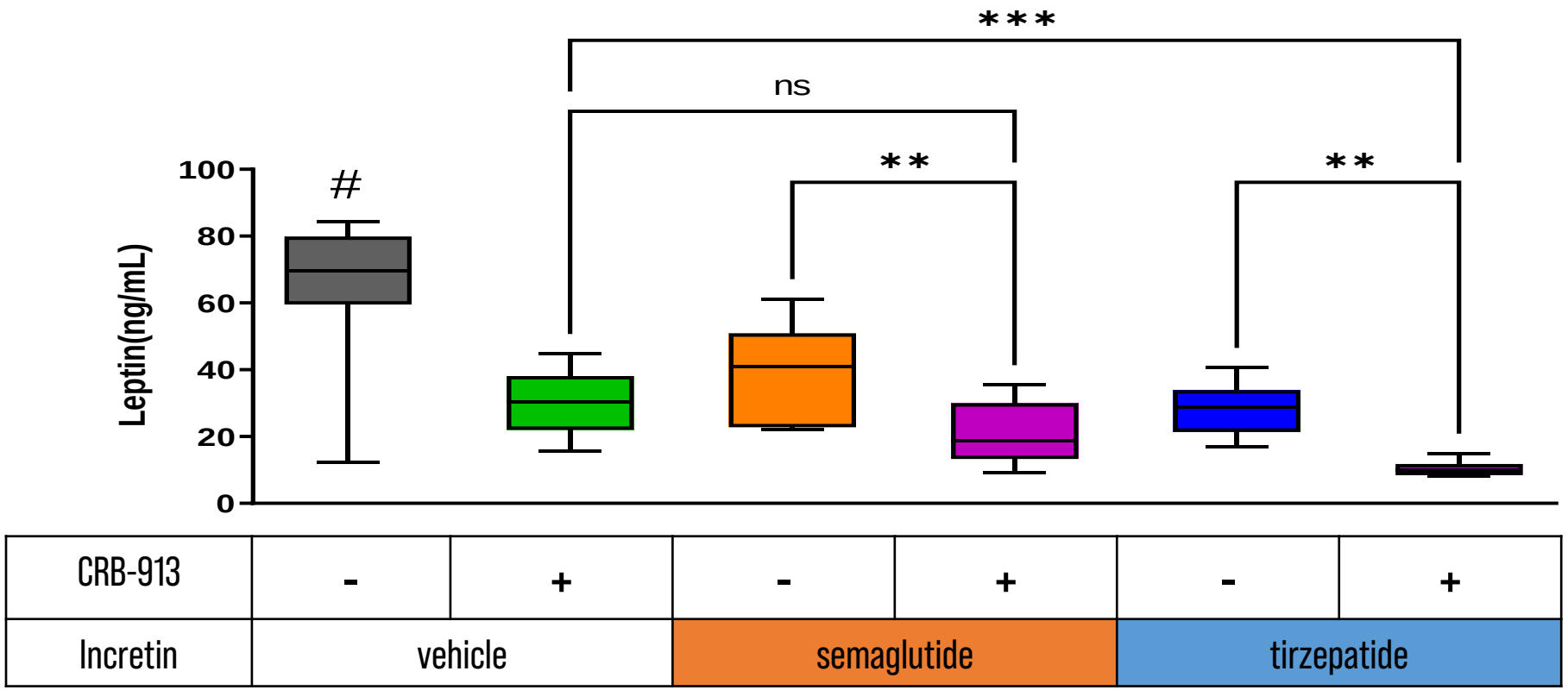
DIO mouse model with C57BL6/J mice (n=10) fed a continuous high fat diet for 22 weeks prior

CB1 and GLP-1 Receptors Cross Talk Provides New Therapies for Obesity. Diabetes, 70, 415-422, 2021

Leptinemia



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All cohorts P < 0.001 compared with vehicle

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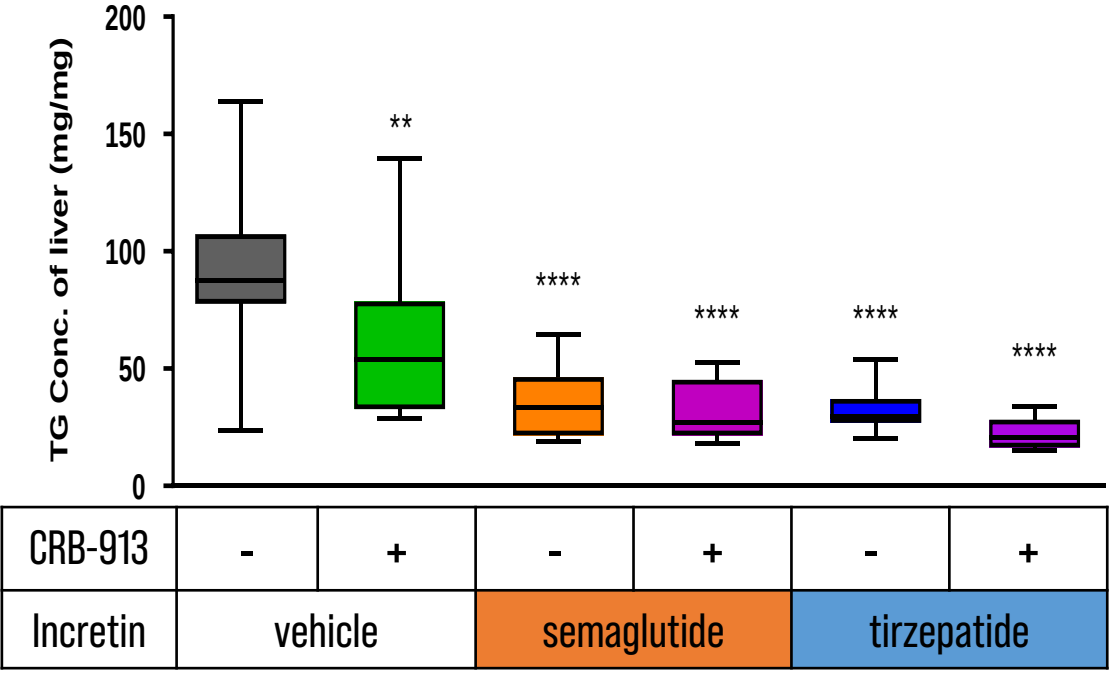
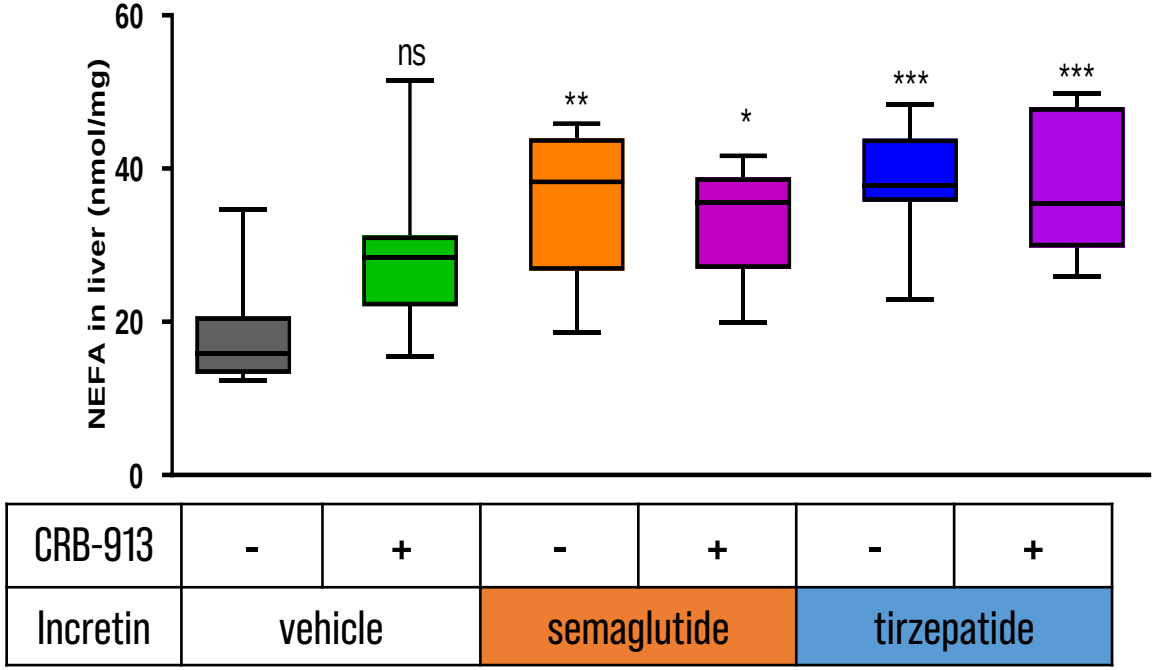
- Determined on Day 29 after 5 h fasting and 2 h post final dose

Liver lipids

Triglycerides (liver)



Non-esterified fatty acid (liver)



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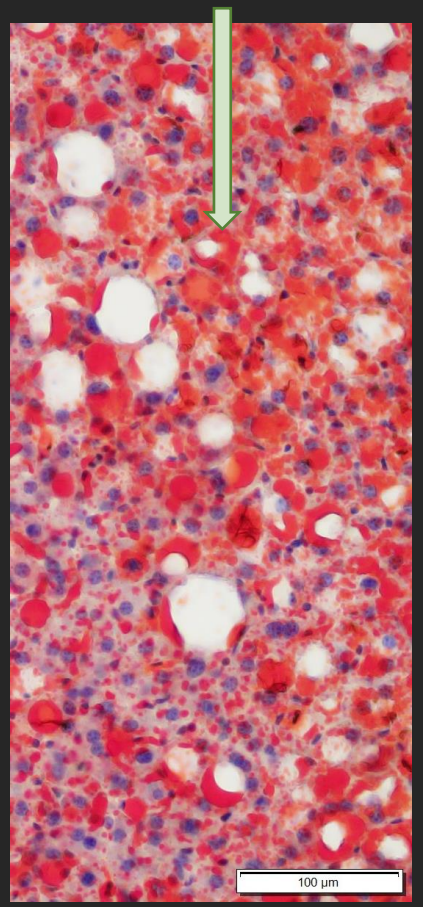
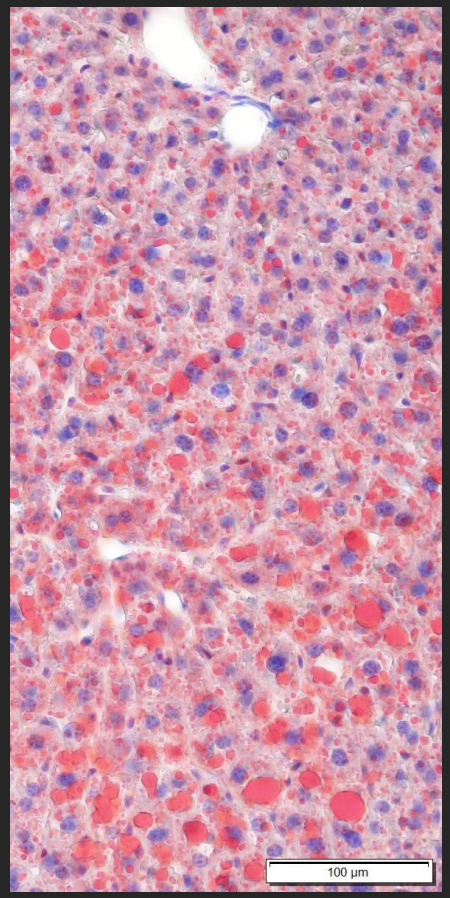
- DIO mouse model with C57BL6/J mice (n=10) fed a continuous high fat diet for 22 weeks prior
- Determined on Day 29 after 5 h fasting and 2 h post final dose

Liver histology

Liver fat

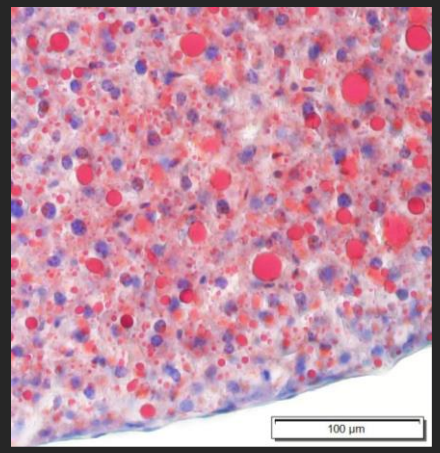


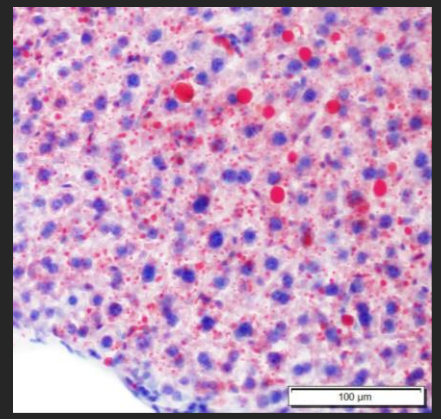
vehicle



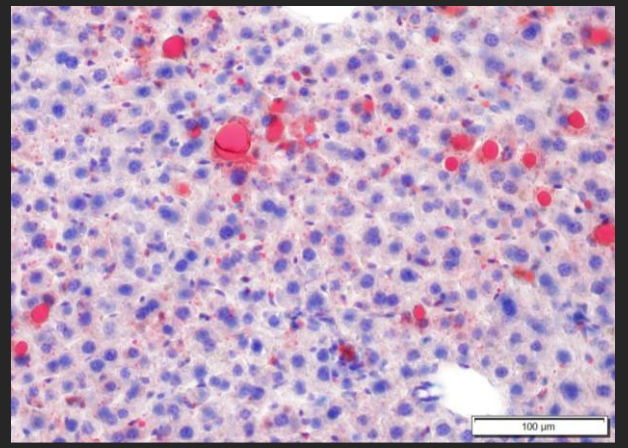
CRB-913
(2.5 mg/kg)

semaglutide
(10 nmol/kg)

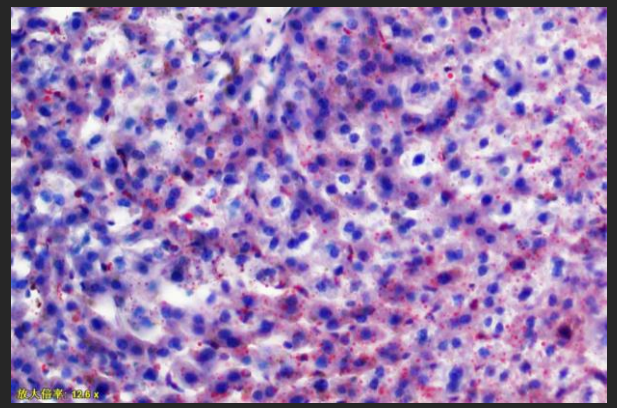




tirzepatide
(5 nmol/kg)



CRB-913 (2.5 mg/kg) +
semaglutide (10 nmol/kg)

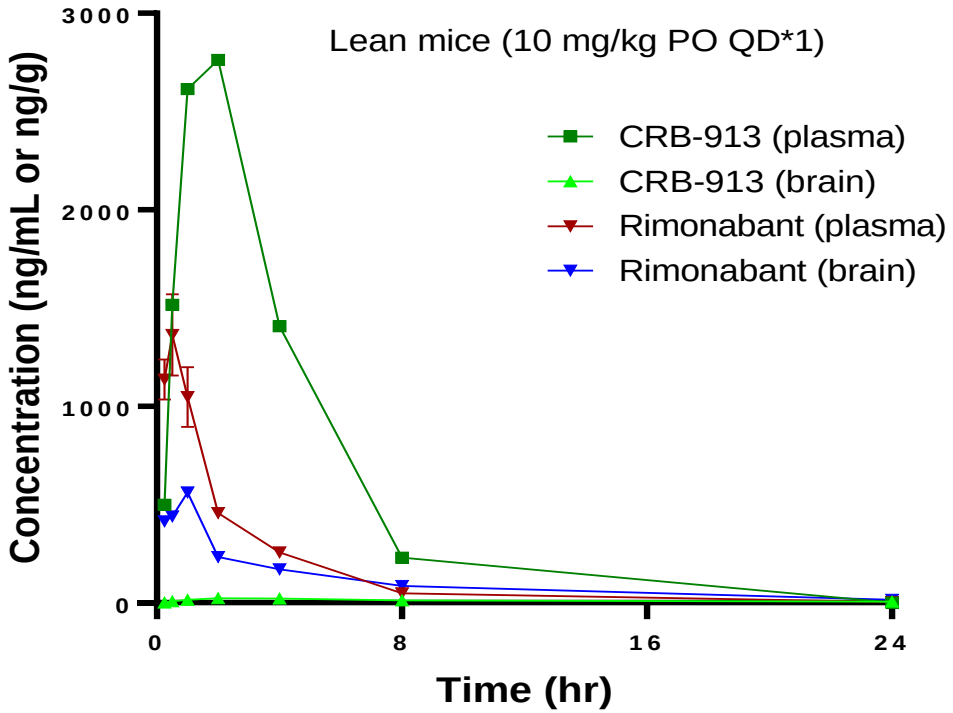


CRB-913 (2.5 mg/kg) + tirzepatide
nmol/kg)

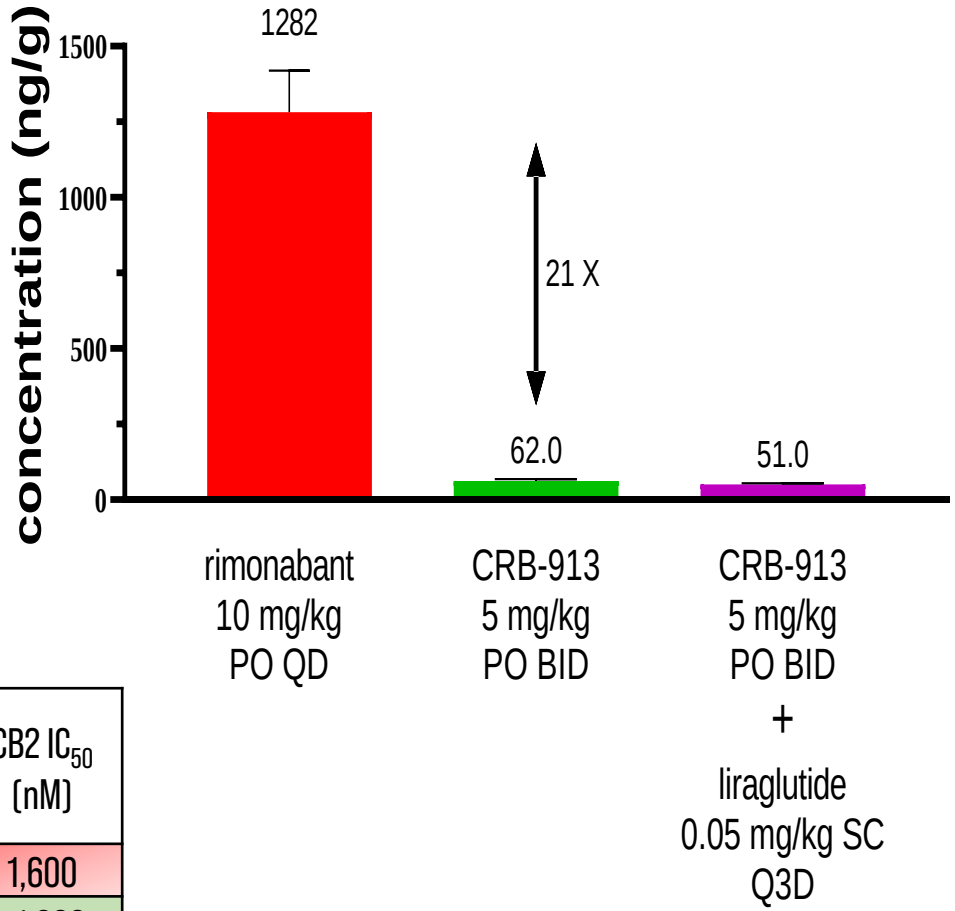
- DIO mouse model with C57BL6/J mice (n=10) fed a continuous high fat diet for 22 weeks prior
- Determined on Day 29 after 5 h fasting and 2 h post final dose
- Liver staining with oil red

CRB-913 PK demonstrates 21-fold lower brain exposure than rimonabant

Lean Mice (PO 1 dose)



Brain con. @ 1hr post dose
DIO Mice (dosing for 20 days)



	CB1 EC_{50} cAMP Inverse Agonist (nM)	CB1 IC_{50} (nM)	CB2 IC_{50} (nM)
Rimonabant	51	4.1	1,600
CRB-913	1.7	1.2	>1,000

CRB-913 Summary

- Oral small molecule CB1 inverse agonist with dose dependent weight loss in preclinical animal models
- Additive efficacy in combination with incretins
- Highly differentiated brain and plasma PK from 1st gen CB1 drugs

Marshall.Morningstar@CorbusPharma.com

Sean.Carroll@CorbusPharma.com