Obesity Week 2023

CRB-913: A Novel Oral Cannabinoid Receptor-1 (CB-1) Inverse Agonist Enhances Tirzepatide and Semaglutide Efficacy in a Diet Induced Obesity Mouse Model

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October 16, 2023

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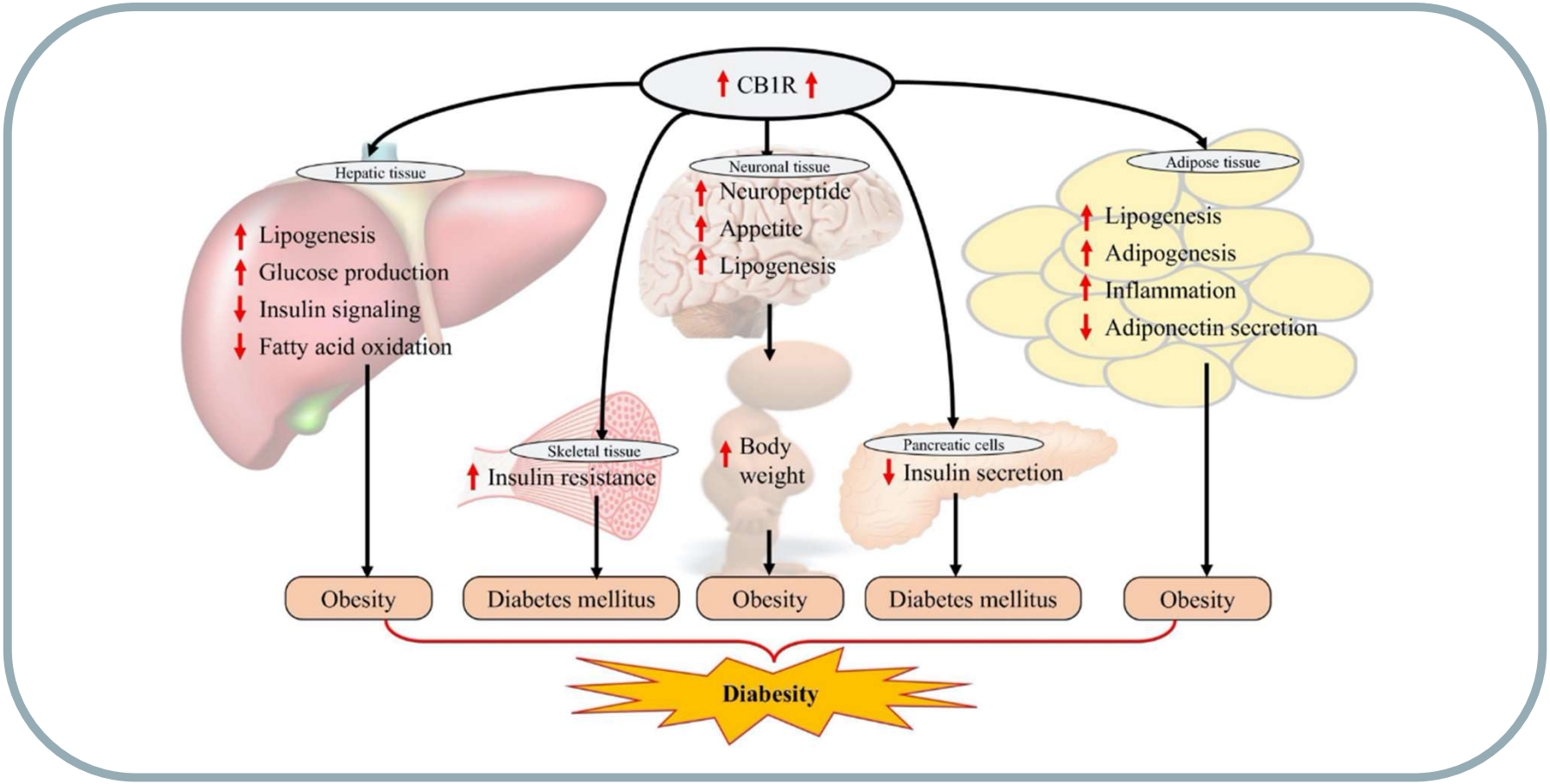
CB1 activation contributes to “Diabesity”

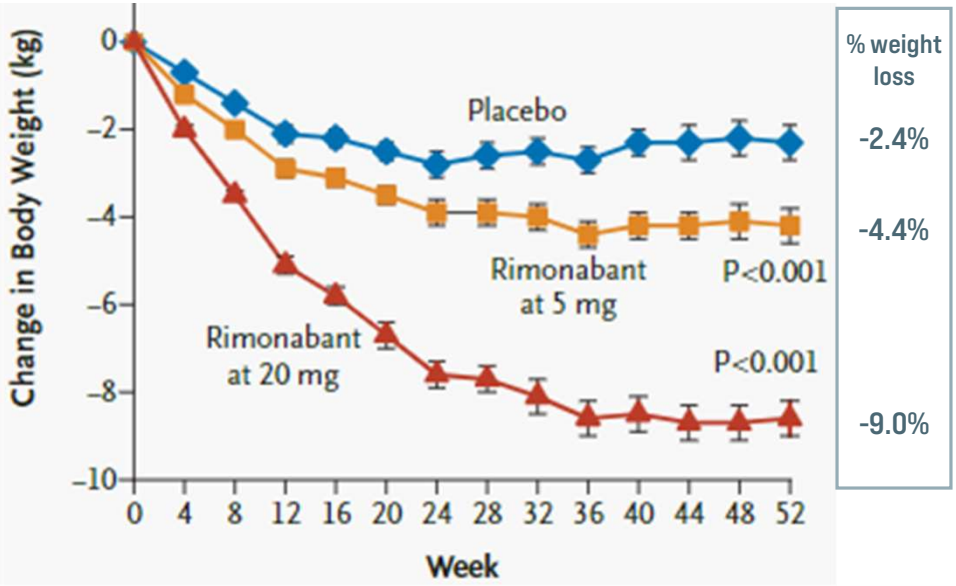


Source(s): Targeting the endocannabinoid system in diabesity: Fact or fiction?, Drug Discovery Today, Deeba et al. Mar 2021.

The CB1 MOA is clinically validated in obesity

Rimonabant[1]

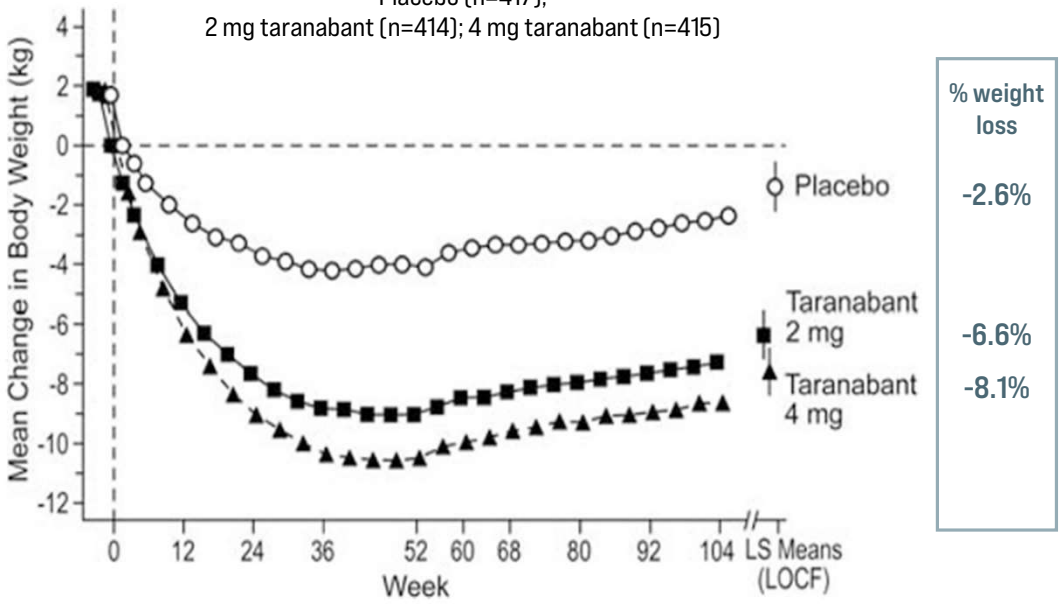
RIO-Lipids Phase 3 study
Placebo (n=342);
5 mg rimonabant (n=345); 20 mg rimonabant (n=346)



Approved (2006) → Withdrawn (2008)

Taranabant[2]

Completed Phase 3 studies (2 and 4 mg) (2 yr)
Placebo (n=417);
2 mg taranabant (n=414); 4 mg taranabant (n=415)



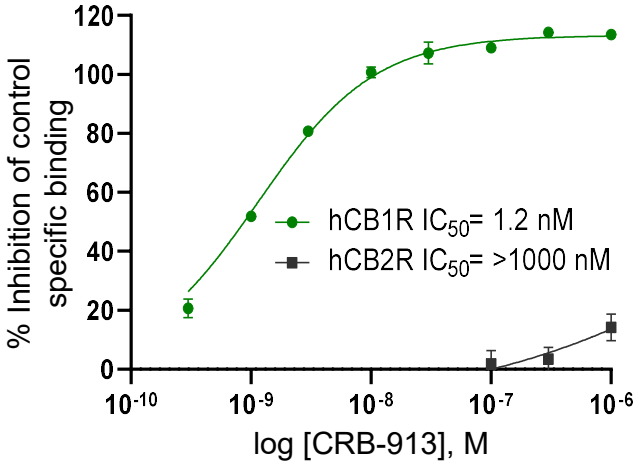
Phase 3 completed

Source(s): 1. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia, Després et al, NEJM, Nov 2005.
2. A clinical trial assessing the safety and efficacy of taranabant, a CB1R inverse agonist, in obese and overweight patients: a high-dose study, Aronne et al, Nature, Feb 2010.

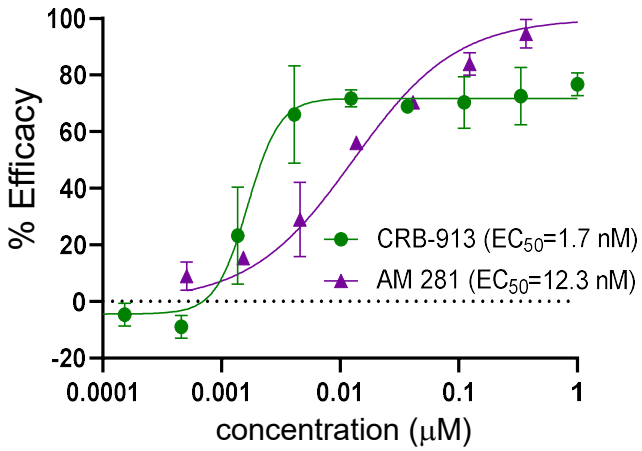
CRB-913 is a potent and selective CB1 receptor inverse agonist

- High selectivity over the CB2 isoform, improved potency across binding and functional assays vs. rimonabant

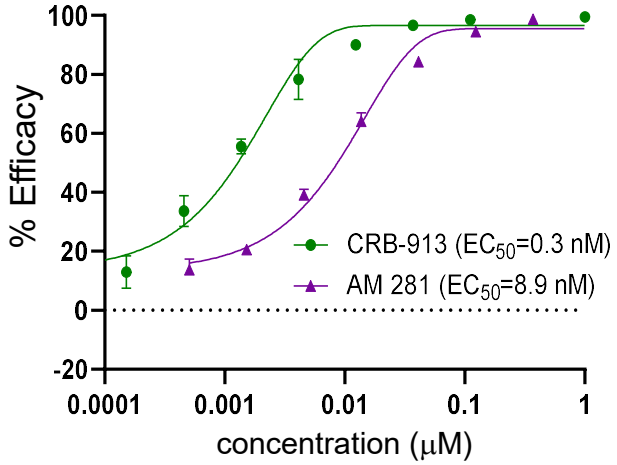
Receptor Binding Affinity



cAMP

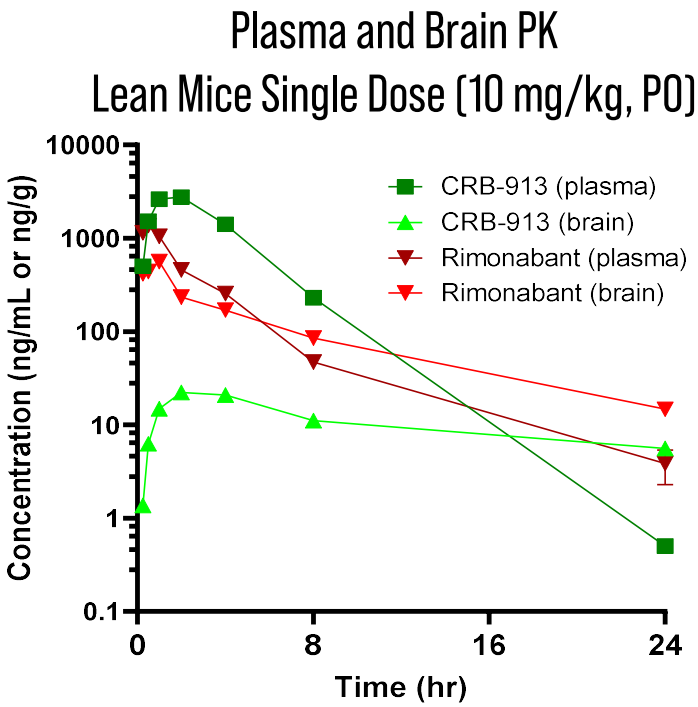


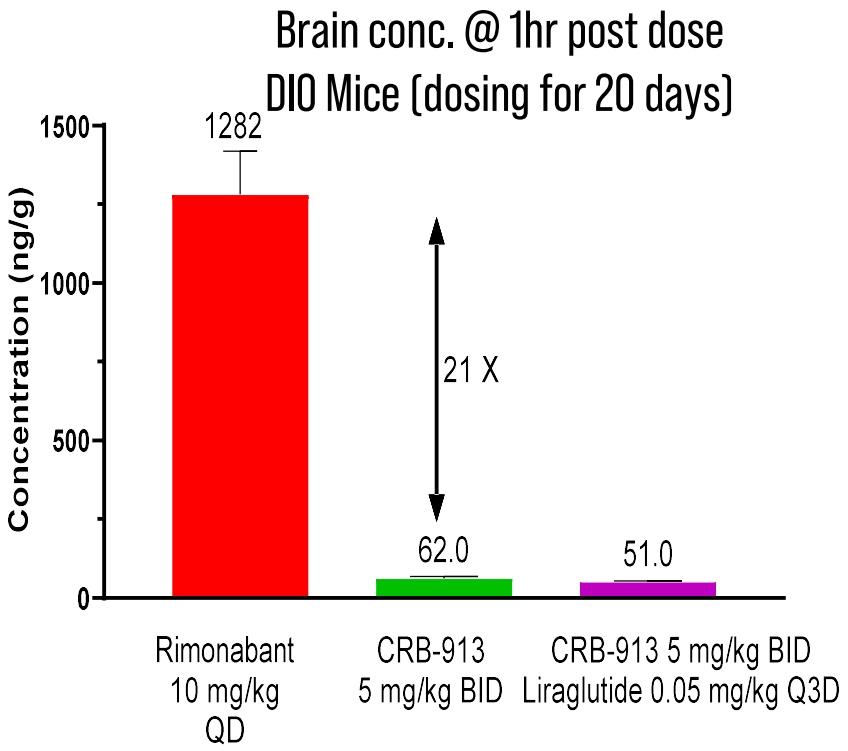
β arrestin



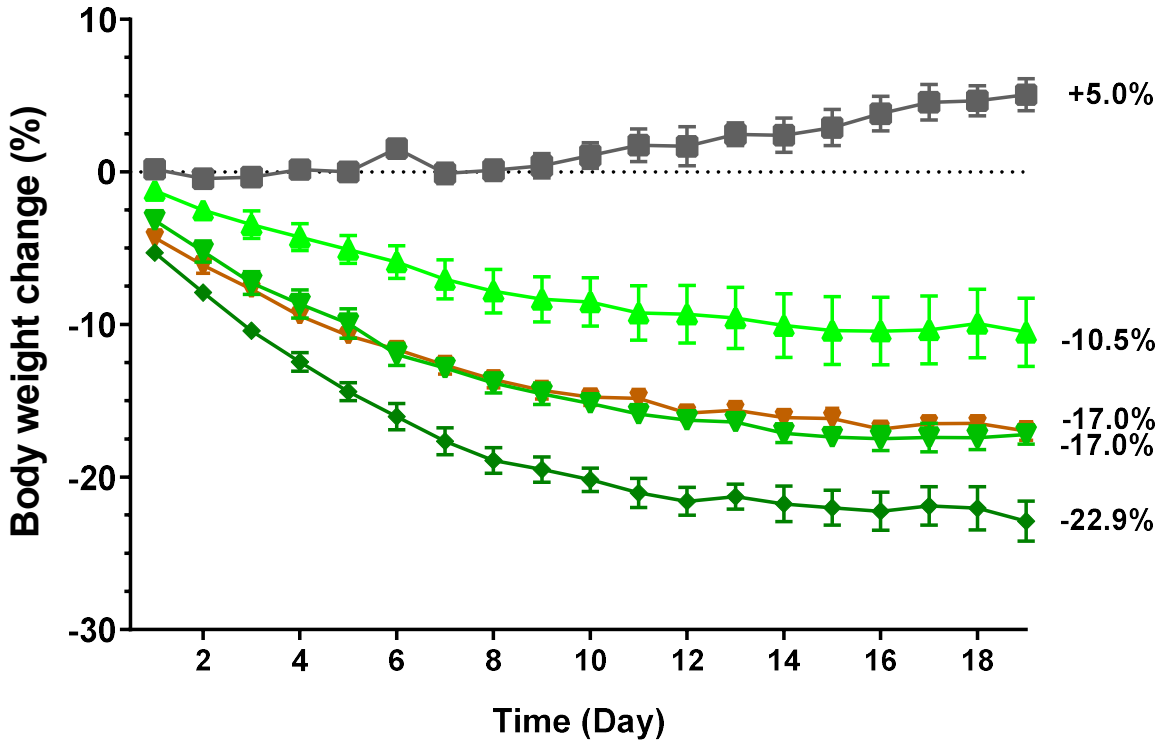
	CB1 EC_{50} cAMP Inverse Agonist (nM)	CB1 IC_{50} (nM)	CB2 IC_{50} (nM)
Rimonabant	51	4.1	1,600
CRB-913	1.7	1.2	>1,000

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





CRB-913 induces significant dose dependent reduction in body weight



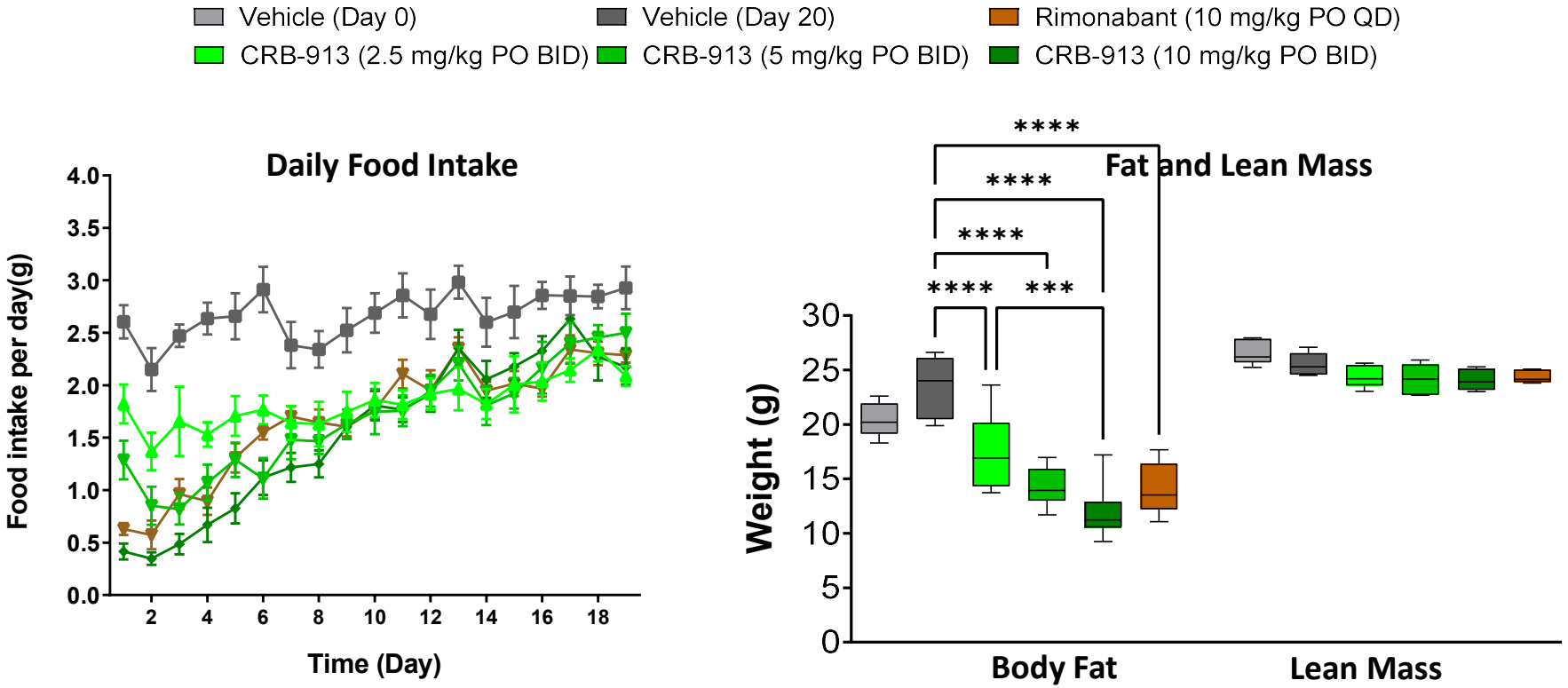
All cohorts P < 0.001 compared with vehicle

Data were presented as Mean ± Sem;Two way ANOVA followed by Dunnett test by Prism GraphPad;n=6

- DIO mouse model with C57BL6/J mice (n=6/gp) fed a continuous high fat diet for 22 weeks prior to treatment with CRB-913

Source(s): Company data on file.

Weight loss is related to reduced food consumption and results in reduced body fat content but not lean mass

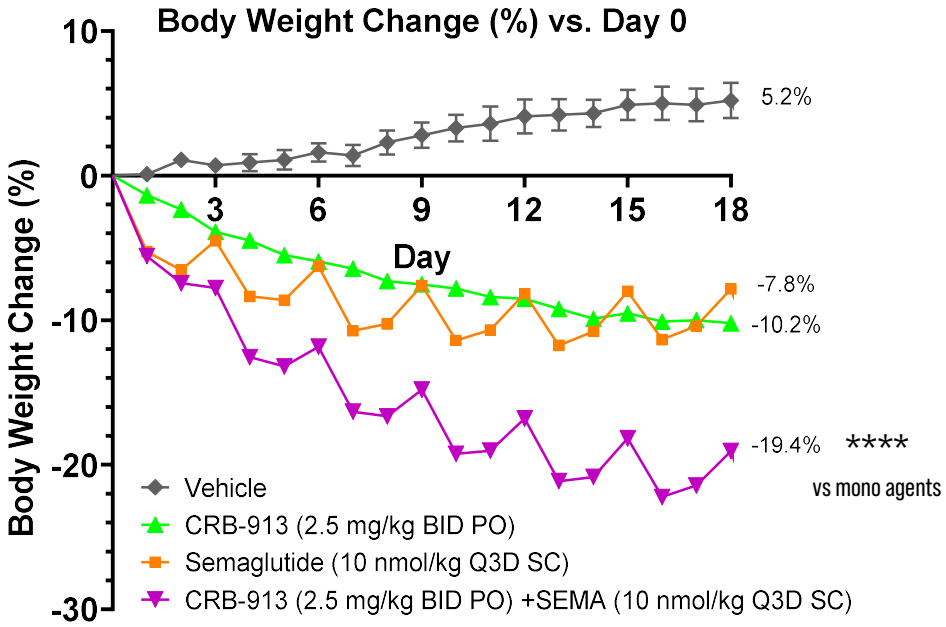


- DIO mouse model with C57BL6/J mice (n=6) fed a continuous high fat diet for 22 weeks prior to CRB-913 treatment
- Body fat by MRI determined on Day 20

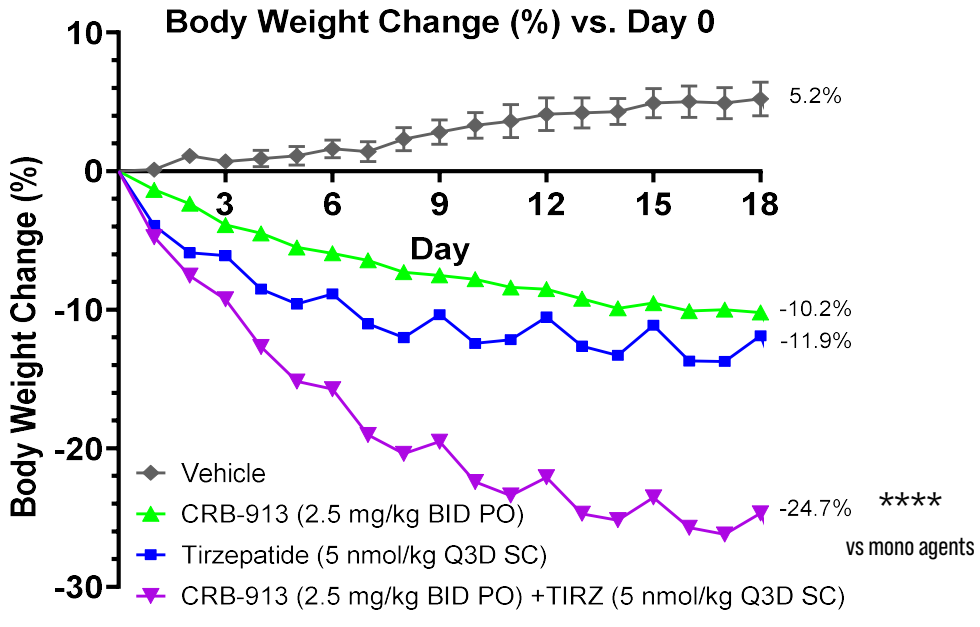
Source(s): Company data on file.

CRB-913: additive weight loss in combination with semaglutide & tirzepatide

semaglutide



tirzepatide

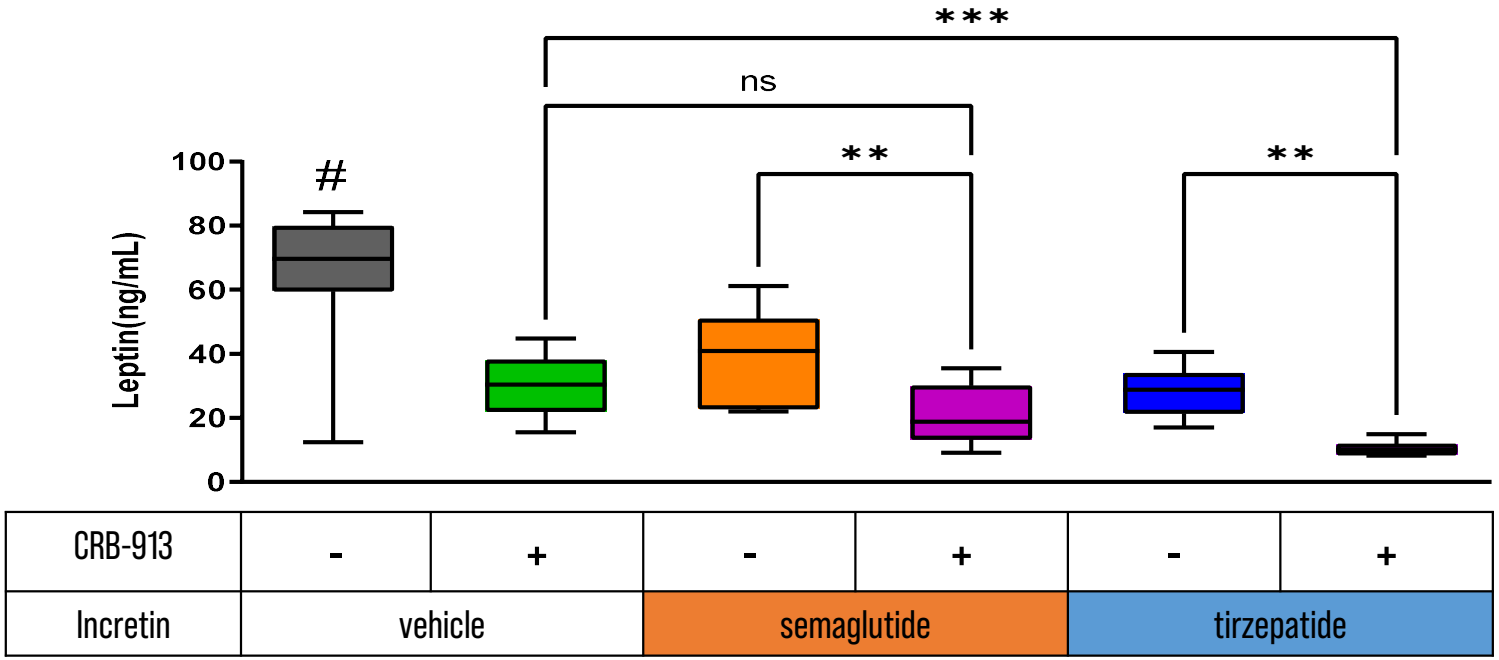


Data were presented as Mean ± Sem;Two-way ANOVA followed by Dunnett test by Prism GraphPad; n=6. *P<0.05,****P<0.0001

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

CRB-913 reduces leptin levels alone and in combination with incretin therapies



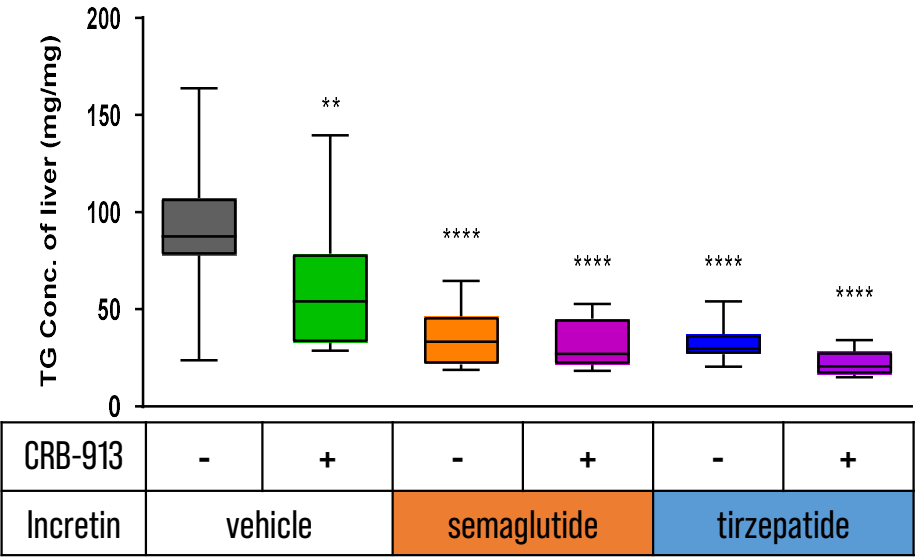
Data were presented as Mean ± Sem;Two-way ANOVA followed by Dunnett test by Prism GraphPad; n=6.
*P<0.05,****P<0.0001

All cohorts P < 0.001 compared with vehicle

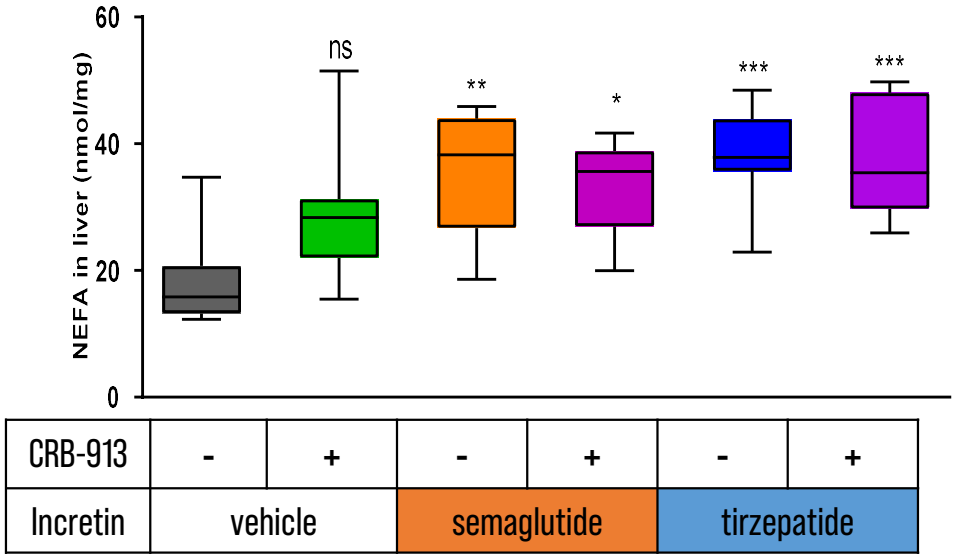
- DIO mouse model with C57BL6/J mice (n=10) fed a continuous high fat diet for 22 weeks prior
- Determined on Day 29 after 5 h fasting and 2 h post final dose

CRB-913 reduces liver triglycerides alone and in combination with incretin therapies

Triglycerides (liver)



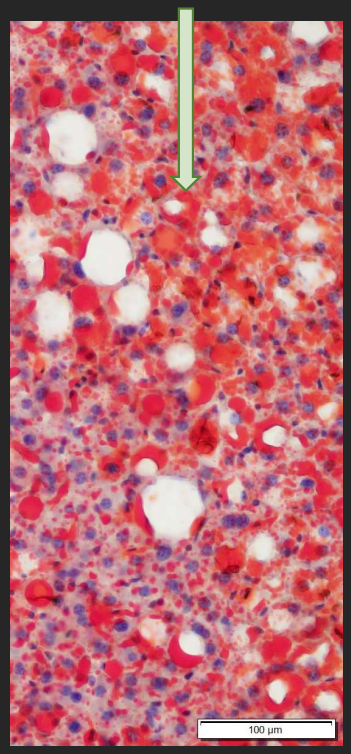
Non-esterified fatty acid (liver)



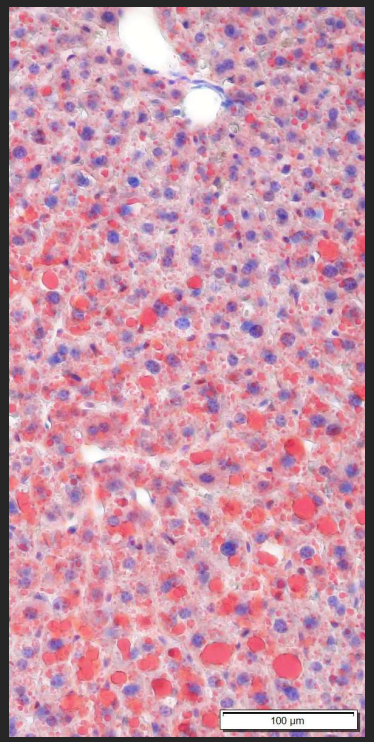
Data were presented as Mean ± Sem; Two-way ANOVA followed by Dunnett test by Prism GraphPad; n=6.
*P<0.05,****P<0.0001 vs Vehicle

- 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

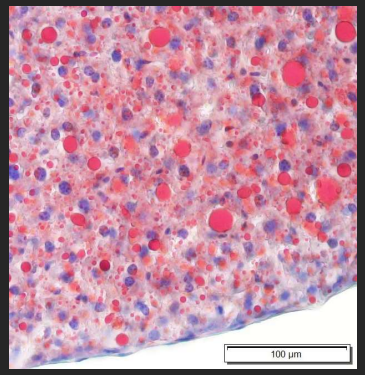
CRB-913 treatment reduces liver fat storage alone and in combination with incretin therapies

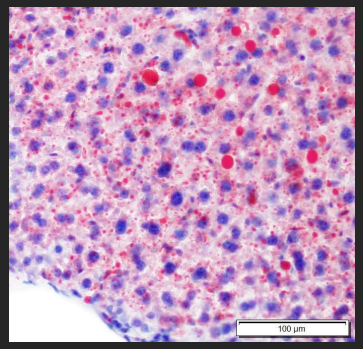


vehicle

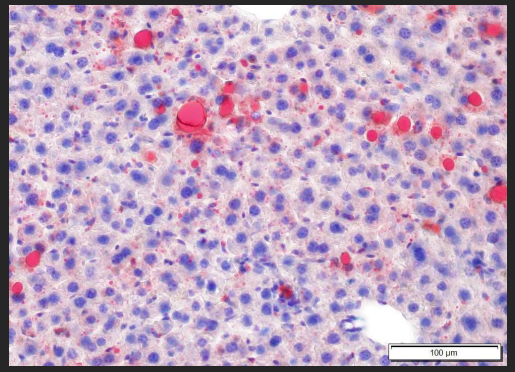


CRB-913
(2.5 mg/kg)

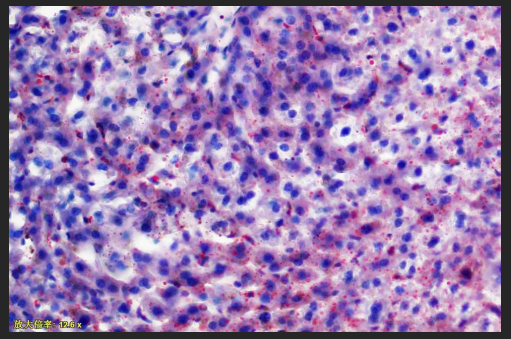




tirzepatide
(5 nmol/kg)



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

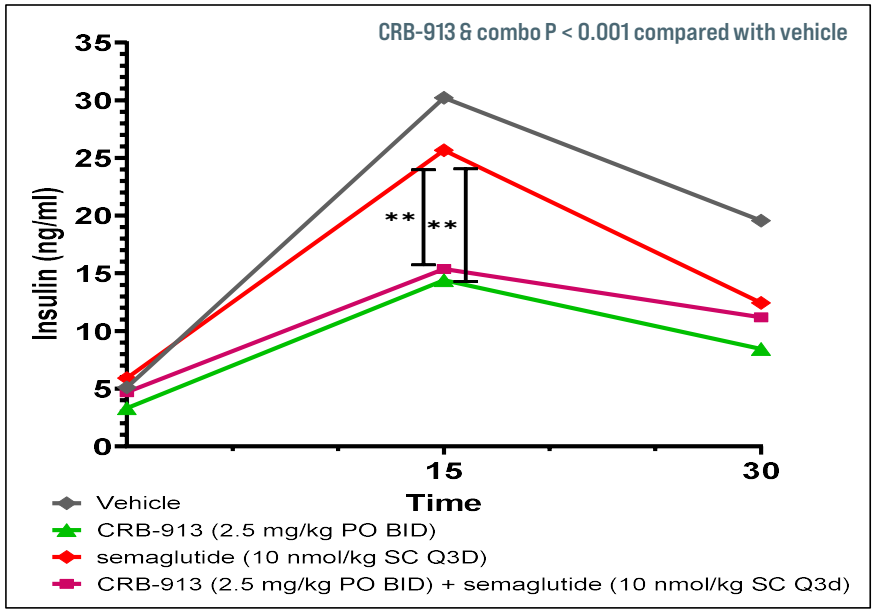


CRB-913 (2.5 mg/kg) + tirzepatide
nmol/kg)

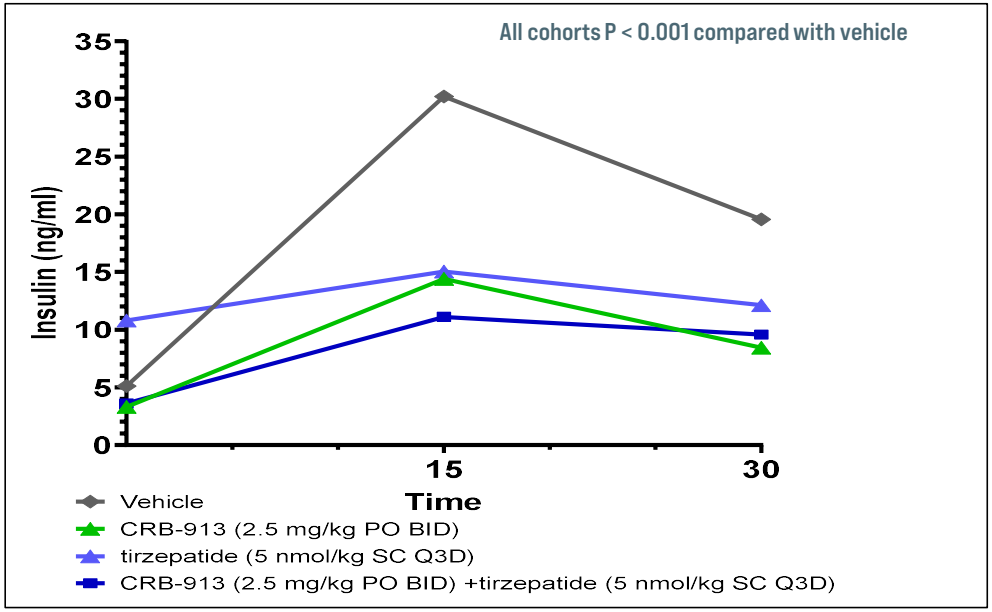
- DIO mouse model with C57BL6/J mice (n=10) fed a continuous high fat diet for 22 weeks prior
- Determined on Day 29 after 5 h fasting and 2 h post final dose
- Liver staining with oil red

CRB-913 reduces peak insulin alone or in combination with semaglutide or tirzepatide in oGTT

semaglutide



tirzepatide



- DIO mouse model with C57BL6/J mice (n=10) fed a continuous high fat diet for 22 weeks prior
- Determined on treatment Day 21 by fasting after evening dosing and 1h post morning dosing
- Oral gavage with glucose at 2g/kg at a dose volume of 5ml/kg

➢ Reduced fasting glucose levels in CRB-913 and incretin treated groups and reduced glucose AUC0-120min

Source(s): Company data on file.

CRB-913 Summary

- Orally available small molecule CB1 inverse agonist with dose dependent weight loss in preclinical animal models, attributed to reduced food intake and body fat content
- Highly differentiated brain and plasma PK from 1st gen CB1 inverse agonists
- Additive efficacy in driving weight loss when administered in combination with incretin therapies
  - Reduced leptinemia, liver lipid storage, and insulin release (oGTT)
- Potential as an adjunctive therapy to improve current incretin regimes or add to novel GLP1/GIP oral therapies in development

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