CRB-913: A Novel Oral Cannabinoid Receptor-1 (CB1R) Inverse Agonist Enhances Tirzepatide and Semaglutide Efficacy in a Diet Induced Obesity Mouse Model

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Poster

Background

- CB1 Receptor is a clinically validated therapeutic target in obesity reducing food intake, body weight, and adiposity[1,2].
- The first approved CB1R inverse agonist, rimonabant, was approved in 2006 in 38 countries for treating obesity over 28K patients in clinical studies and 78K patients post marketing approval.
- Post hoc analysis by FDA during the FDA's review noted a potential (non-statistical) increase in suicidality risk leading the FDA Adcom to vote against approval. Subsequently rimonabant was withdrawn worldwide from the market.
- Peripherally restricted CB1R inverse agonists aim to mitigate CNS issues by lowering high brain exposure common with rimonabant and other first generation CB1-R inverse agonists while blocking the effects of endocannabinoids linked to leptin resistance, insulin sensitivity, fat storage and energy expenditure in peripheral tissues.
- CRB-913 is an orally available next generation high potency CB1R inverse agonist which aims to mitigate CNS-related effects by minimizing brain exposure while retaining significant efficacy to induce weight loss.
- Incretin receptor modulators, including semaglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, and tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP-1) receptor and GLP-1 receptor agonist, have emerged as important therapies for treatment of adults with obesity, or overweight with weight-related comorbidities such as diabetes.
- The present study examines the effects of CRB-913 alone and in combination with tirzepatide and semaglutide in a DIO efficacy study across multiple endpoints including weight loss, food intake, body fat composition, leptin and insulin levels, and liver fat storage[3].

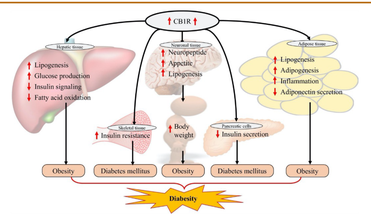

Figure 1: The CB1 pathway modulates appetite and energy metabolism via signaling in the brain and peripheral tissues. CB1 activation results in increased appetite and body weight, liver lipid storage, lipogenesis, and insulin resistance[4].

References

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2. Proietto J, Rissanen A, Harp JB, et al. A clinical trial assessing the safety and efficacy of the CB1R inverse agonist taranabant in obese and overweight patients: low-dose study. Int J Obes (Lond). 2010;34(8):1243-1254.
3. Morningstar M, Kolodziej A, Ferreira S, Blumen T, Brake R, and Cohen Y. Novel CB1R Inverse Agonist CRB-913 Enhances Efficacy of Tirzepatide, Semaglutide and Liraglutide in the DIO Mouse Model. Obesity DOI: 10.1002/oby.23902
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Results

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

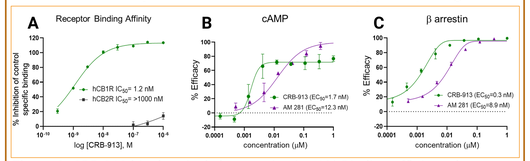


Figure 2: CRB-913 biochemical characterization **(A)** Binding affinity to human CB1R and CB2R (hCB1R- green, hCB2R - black) as determined by the displacement of a radiolabeled cannabinoid agonist. **(B)** Inhibition by CRB-913 (green) or positive control AM281 (purple) using DiscoverX cAMP secondary messenger pathway assay (C) Inhibition by CRB-913 (green) or AM281 (purple) using PathHunter β-arrestin assay.

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

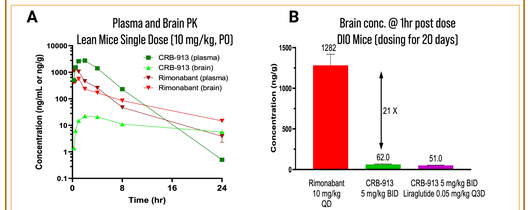


Figure 3: CRB-913 and rimonabant PK and brain exposure **(A)** Plasma and brain concentrations (mean ±SEM) determined by LC-MS, after a single 10 mg/kg PO dose in lean male mice (N=3 mice/group) **(B)** Brain concentrations mean ± SEM) 1 hr post-dose of rimonabant and CRB-913 after 35 days repeat PO dosing in DIO male mice (N=10 mice/group). Coadministration of CRB-913 (PO) with liraglutide (SC) did not alter CRB-913 brain exposure

CRB-913 induces significant dose dependent reduction in body weight

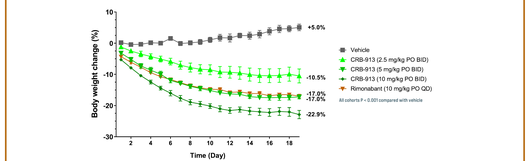


Figure 4: Efficacy of CRB-913 monotherapy in the DIO mouse model. DIO mice were treated daily with vehicle, rimonabant (10 mg/kg PO QD), or CRB-913 (2.5, 5, or 10 mg/kg PO BID, green curves) for 20 days. Body-weight changes were analyzed by two-way ANOVA repeated measurements with the Tukey multiple comparison test. Post-test results were statistically significant (P<0.001) for all cohorts compared to vehicle. All data are mean ±SEM from 6 mice/group

Weight loss is related to reduction in body fat content but not lean mass

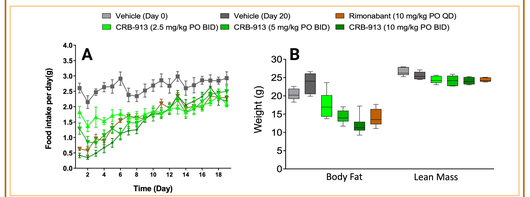
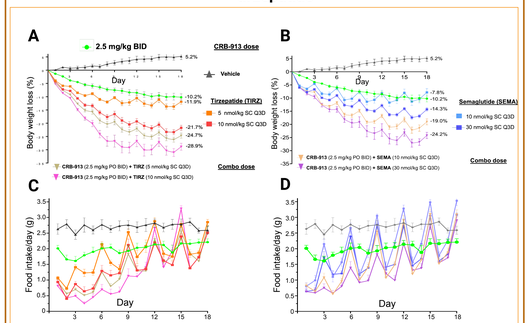


Figure 5: CRB-913 DIO mouse monotherapy effects on **(A)** Food intake and **(B)** Lean mass and fat mass at Day 0 (predosing) and Day 20 (end of study) measured by EchoMRI-130 body composition analyzer. Fat and lean mass change were analyzed by two-way ANOVA comparison to Vehicle Day 20, followed by Dunnett test. All results on Day 20 were p<0.001

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



CRB-913 PO BID	Tirzepatide SC Q3D		Semaglutide SC Q3D	
	5 nmol/kg	10 nmol/kg	10 nmol/kg	30 nmol/kg
0 mg/kg		-11.9%	-21.7%	-7.8%	-14.3%
2.5 mg/kg	-10.2%	-24.7%	-28.9%	-19.0%	-24.2%
5 mg/kg	-18.5%	-28.1%	-32.6%	-24.3%	-26.7%

Figure 6: Efficacy in **(A-B)** weight loss and **(C-D)** food intake of CRB-913 (2.5 mg/kg PO BID) in combination with **(A,C)** semaglutide (10 & 30 nmol/kg IP Q3D) or **(B,D)** tirzepatide (5 & 10 nmol/kg IP Q3D) in male C57BL/6J DIO mice treated daily for 28 days (n=8 mice/group). Food intake for each animal was recorded before dosing in the morning. **(E)** Table of body weight changes at Day 18 for CRB-913 (2.5 &5 mg/kg) and incretin monotherapies, and CRB-913 plus incretin combination therapies. All data are mean ±SEM from 8 mice/group and were statistically significant (p<0.0001) by two-way ANOVA repeated measurements with the Tukey multiple comparison test at individual timepoints.

CRB-913 reduces liver triglycerides, NEFA, and liver fat storage alone and in combination with incretin therapies

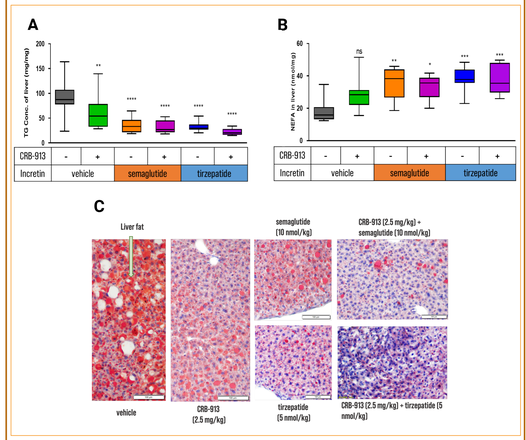


Figure 7: (A) Terminal fasting triglyceride (TG) and **(B)** non-esterified fatty acid (NEFA) levels (Mean ± Sem) in DIO mice (n=8/gp) measured on Day 35 after fasting for 5 hours and 1 hour after CRB-913 and incretin administration. Data significance evaluated by two-way ANOVA followed by Dunnett test. *P<0.05; **p<0.01, ***p<0.001, ****P<0.0001 **(C)** Reduction of liver fat deposits. Staining of hepatic lipids with Oil Red O on frozen sections of DIO mice. Stained areas from randomly selected liver slices at 20X magnification with scale at 100 μm.

CRB-913 reduces ALT and AST alone and in combination with incretin therapies

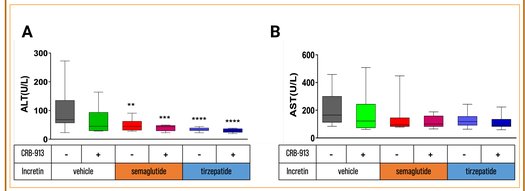


Figure 8: Liver function tests of DIO mice treated daily with vehicle or CRB-913 (2.5 mg/kg PO BID) alone or in combination with semaglutide (10 nmol/kg SC Q3D) or tirzepatide (5 nmol/kg SC Q3D) for 35 days. **(A)** ALT levels and **(B)** AST levels were measured at end of study and analyzed by one-way ANOVA vs. vehicle (**p<0.01; ***p<0.001; ****p<0.0001). Data reported are Mean ± Sem for n=8 mice/group.

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

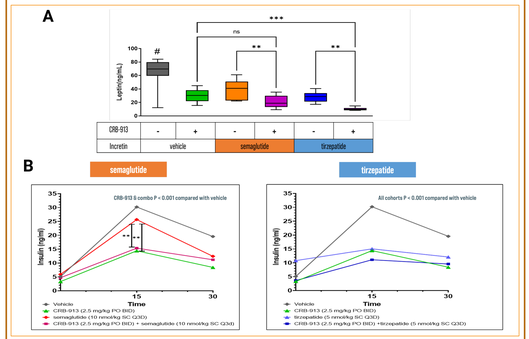


Figure 9: (A) Leptin levels and **(B)** insulin response following glucose challenge in DIO mice treated with CRB-913 (2.5 mg/kg BID PO), Semaglutide (10 nmol/kg q3d IP), Tirzepatide (5 nmol/kg q3d IP) alone or in combination. Leptin levels were measured on Day 28 after 5 h fasting and 2 h post final dose in DIO mice. Effects on insulin release during an oral glucose tolerance test (2 g/kg, 5 mL/kg by oral gavage) in DIO mice on treatment Day 19 following overnight fasting, 1h post morning dosing. Data are presented as Mean ± Sem; n=8/gp. Two-way ANOVA followed by Dunnett test. **p<0.01, ***p<0.001, ****p<0.0001, # All cohorts compared with vehicle.

Conclusions

- CRB-913 is an orally bioavailable, highly potent inverse agonist of CB1R (1.2 nM) with high selectivity over the CB2 receptor isoform.
- CRB-913 achieved comparable weight loss to rimonabant at an equivalent daily dose, but with 21-fold less brain exposure.
- Combining CRB-913 with incretin receptor agonists tirzepatide or semaglutide additively increased weight loss effects highlighting the potential of combining therapies that target these orthogonal pathways.
- CRB-913 in combination with tirzepatide or semaglutide lowered liver fat content resulting in improved liver function (lower AST/ALT).
- CRB-913 reduced peripheral leptin levels which were further reduced in combination with incretin therapies
- CRB-913 treatment reduced insulin secretion in response to an oral glucose challenge, suggesting improvements in insulin sensitivity.
- The convergent physiological benefits of CRB-913 and incretin analogs could offer patients improved obesity management, potentially enhancing the efficacy of current therapies.
- CRB-913 is poised for advancement into clinical trials exploring its safety and efficacy, both as monotherapy and in combination with incretin receptor agonist therapy.