Induction and maintenance regimens with CB1 inverse agonist CRB-913 and semaglutide in DIO mice

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BACKGROUND

- Inverse agonism of the cannabinoid receptor type 1 (CB1) is a clinically validated mechanism for promoting weight loss and improving related clinical outcomes.[1]
- Clinical development of first generation CB1 inverse agonists was halted following the rejection of rimonabant by the US Food and Drug Administration in 2007, owing to a perceived risk around suicidal ideation.[2,3]
- A new generation of peripherally restricted CB1 inverse agonists (including monlunabant, CRB-913 and INV-347) is emerging as a promising alternative.[4,5]
- We previously reported the preclinical efficacy of CRB-913 in diet-induced obese (DIO) mice with twice daily (BID) oral dosing both as monotherapy and when co-administrated with liraglutide, semaglutide or tirzepatide.[6]
- Here we present additional preclinical data on CRB-913, including comparisons with monlunabant and weight loss following semaglutide induction and CRB-913 maintenance.

Part 1: Dose escalation studies

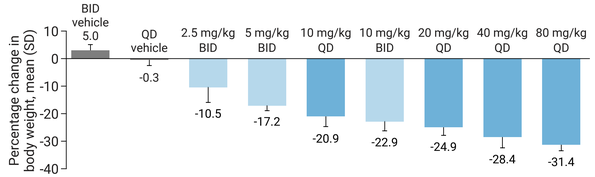
METHODS

- In two studies using the same protocol, 5-week-old male C57BL/6J mice were fed a high-fat pelleted diet (D12492, Rodent Diet with 60 kcal% fat, Research Diets, Inc.) for at least 13 weeks before dosing.
- At baseline, animals were randomized to receive vehicle or CRB-913 by oral gavage for 19 days.
  - In the first study of BID dosing, mice received 2.5 mg/kg, 5 mg/kg or 10 mg/kg of CRB-913 or vehicle (n = 6 for each group).
  - In the second study of once-daily (QD) dosing, mice received 10 mg/kg, 20 mg/kg, 40 mg/kg or 80 mg/kg of CRB-913 or vehicle (n = 10 for each group).
- The studies were conducted with a 12-hour dark/12-hour light cycle such that dosing coincided with the start of the dark cycle. Individual body weight was measured daily.

RESULTS

- At day 19, dose-related decreases in weight from baseline observed for all doses of CRB-913 across the 16-fold dose range (10.5% with 2.5 mg/kg BID to 31.4% with 80 mg/kg QD) (**Figure 1**).
  - Allometrically, this dose range corresponds to human-equivalent doses of 30 mg/day to over 450 mg/day.
- Extended treatment with the 80 mg/kg dose resulted in weight loss of 38.6% at day 28 (data not shown).
- Body weight changes at a given total daily dose were equivalent, regardless of the dosing frequency.

Figure 1. Change from baseline in body weight across the CRB-913 dose range



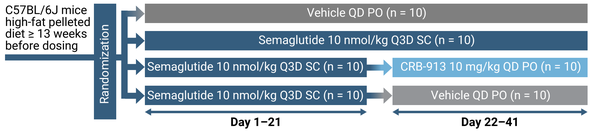
BID dosing groups, n = 6; QD dosing groups, n = 10.
BID, twice daily; QD, once daily; SD, standard deviation.

Part 2: Semaglutide/CRB-913 induction/maintenance study design

METHODS

- Five-week-old male C57BL/6J mice were fed a high-fat pelleted diet (D12492, Rodent Diet with 60 kcal% fat) for at least 13 weeks before dosing.
- Animals were group-housed (n = 5) throughout the study and habituated to the dose procedure with vehicle for 1 week before drug administration.
- Mice were randomly assigned to one of four groups (n = 10 per group) balanced with respect to body weight and levels of fasting blood glucose, alanine transferase and low-density lipoprotein cholesterol (**Figure 2**).

Figure 2. Semaglutide/CRB-913 induction/maintenance study design



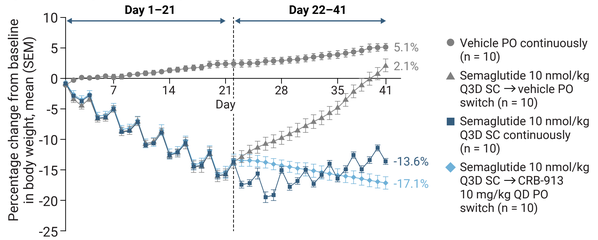
PO, orally; Q3D, every 3 days; QD, once daily; SC, subcutaneously.

- During the first 21 days of the study, three groups received semaglutide 10 nmol/kg subcutaneously every 3 days and the other group received vehicle only.
- From day 22 to day 41, of the three groups of animals that received semaglutide up to day 21, one received CRB-913 10 mg/kg QD by oral gavage, one continued semaglutide and one received vehicle.
- The study was conducted with a 12-hour dark/12-hour light cycle such that dosing coincided with the start of the dark cycle. Individual body weight data were collected daily.
- Fat mass was measured using dual energy X-ray absorptiometry (DEXA) at day 0 and at day 41.
- Differences from day 0 to day 41 in changes in body weight and body fat between treatment groups were analyzed using a two-way and one-way analysis of variance (ANOVA), respectively.

RESULTS

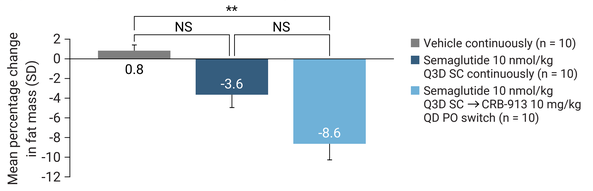
- At day 21, treatment with semaglutide 10 nmol/kg resulted in a mean weight loss of up to 13.7% (**Figure 3**).
- Withdrawal of semaglutide and its replacement with vehicle resulted in rapid rebound weight gain at a similar rate to the initial weight loss (**Figure 3**).
  - Weight loss achieved in mice receiving semaglutide during days 1–21 had disappeared only 17 days after switching to vehicle.
- Switching to CRB-913 from semaglutide at day 22 resulted in significantly greater additional weight loss than continuous semaglutide (weight loss from day 0 to day 41, 17.1% vs 13.6%, $p < 0.01$; **Figure 3**).
- In mice treated with semaglutide continuously, weight loss at day 21 (13.7% versus day 0) was almost the same as at day 41 (13.6%) (**Figure 3**).
- Mice switched to CRB-913 from semaglutide had significantly reduced fat mass compared with those in the vehicle group (change from day 0 to day 41 of −8.6% versus 0.8%, $p < 0.01$; **Figure 4**).
  - The equivalent change in mice receiving semaglutide continuously for 41 days was −3.6% and was not significantly different to vehicle.
- The reduction in mean fat mass change more than doubled for the mice switched to CRB-913 compared with those receiving semaglutide continuously.

Figure 3. Change in body weight



PO, orally; Q3D, every 3 days; QD, once daily; SEM, standard error of the mean.

Figure 4. Change in fat mass from day 0 to day 41



**p < 0.01.
NS, not significant; PO, orally; Q3D, every 3 days; QD, every day; SC, subcutaneously; SD, standard deviation.

Part 3: CB1 selectivity and pharmacokinetics of CRB-913, monlunabant and rimonabant

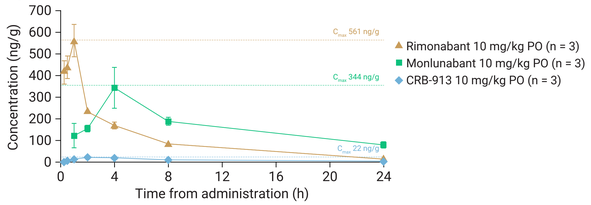
METHODS

- Lean C57BL/6J mice were administered a single 10 mg/kg dose of CRB-913, monlunabant or rimonabant, by oral gavage (n = 3 for each compound).
- CB1 inverse agonist activity was evaluated with the DiscoverX Path Hunter and Hit Hunter platform assays to determine the half maximal inhibitory concentrations (IC_{50}) for β-arrestin recruitment and cyclic adenosine monophosphate (cAMP) production, respectively.
- Drug plasma and brain concentrations were measured by liquid chromatography–mass spectrometry against a set of standards and quality controls in a matched matrix.

RESULTS

- Despite similar peripheral exposure, CRB-913 demonstrated 15-fold lower brain exposure than monlunabant when measured by maximum concentration (C_{max}), or area under the curve from 0 to 24 hours (AUC_{0-24}) (**Figure 5**, **Table 1**).
- Plasma:brain AUC_{0-24} ratios were 50 to 1 for CRB-913 versus 5 to 1 for monlunabant (**Table 1**).
- IC_{50} values for cAMP and β-arrestin were similar for CRB-913 and monlunabant (**Table 1**).

Figure 5. Concentrations of CRB-913, monlunabant and rimonabant in the brain



C_{max}, maximum concentration; PO, orally.

Table 1. Pharmacodynamic and pharmacokinetic properties of CRB-913, monlunabant and rimonabant

	Biochemical parameters		Plasma		Brain	
	cAMP IC_{50}, nM	β-arrestin IC_{50}, nM	C_{max}, ng/mL	AUC_{0-24}, ng·h/mL	C_{max}, ng/g	AUC_{0-24}, ng·h/g
CRB-913 (n = 3)	3.56	0.37	2763	13 260	22	265
Monlunabant (n = 3)	3.69	0.31	2663	18 979	344	3855
Rimonabant (n = 3)	4.46	8.26	1362	3534	561	2515

AUC_{0-24}, area under the curve from 0 to 24 hours; cAMP, cyclic adenosine monophosphate; C_{max}, maximum concentration; IC_{50}, half-maximal inhibitory concentration.

SUMMARY AND CONCLUSIONS

- CRB-913 QD dosing had similar weight loss effects to BID dosing, lending itself to the same dosing regimen as other CB1 inverse agonists.
- Weight loss did not plateau over the 19-day treatment period with CRB-913 dose escalation from 2.5 mg/kg BID to 80 mg/kg QD (16-fold range), with a maximum weight loss of 31% achieved.
- Switching to CRB-913 after 21 days of semaglutide treatment led to a statistically significant additional weight loss at day 41 compared with continuous semaglutide treatment.
  - DEXA data indicate that the additional weight loss was driven primarily by a doubling of fat mass loss after the switch to CRB-913.
- CRB-913 brain exposure (C_{max} and AUC_{0-24}) was 15 times lower than that observed for monlunabant at the same dose, whereas peripheral exposures were similar for both agents.
- CRB-913 is a highly peripherally restricted CB1 inverse agonist that demonstrates potential for clinical use as monotherapy, maintenance therapy or in combination with an incretin analog.
- CRB-913 is under preclinical development to enable anticipated first-in-human studies in 2025.

References

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Disclosures

MM, **AK** and **YC** are employees of and hold stock in Corbus Pharmaceuticals Inc.

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