Efficacy, safety and tolerability of CRB-913 in the phase 1b CANYON-1 study

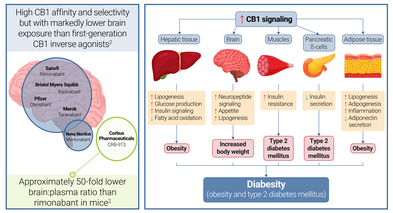
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BACKGROUND

- The cannabinoid receptor type 1 (CB1) is a G protein-coupled receptor with a well-established role in obesity and metabolism, and is abundant in the brain and in peripheral metabolic organs including the liver, pancreas, muscles and adipose tissue. This insight led to the development of the first-generation CB1 inverse agonists for the treatment of obesity two decades ago.[1]
- Rimonabant, the first-in-class brain-penetrant CB1 inverse agonist, was approved for use in people with obesity in the EU in 2006. However, in 2007, a US FDA advisory panel voted not to recommend approval in the USA based on a retrospective analysis that suggested a risk of depression and increased suicidal ideation. The drug was withdrawn worldwide in 2008, and the development of similar drugs was abandoned.[1,2]
- Recently, the peripherally restricted CB1 inverse agonist CRB-913 was designed to have minimal brain penetration and exert its actions via peripheral CB1.[2]
- CRB-913 has been shown to have a 50-fold lower brain:plasma ratio than rimonabant in mice (**Figure 1**).[2]
- In a phase 1a single ascending dose and multiple ascending dose study in healthy volunteers, CRB-913 demonstrated promising safety and tolerability.
- Here we report safety and preliminary efficacy data from the CANYON-1 phase 1b study of nondiabetic adults with obesity who received CRB-913 or placebo once daily for 12 weeks.

Figure 1. CRB-913 is a novel, peripherally restricted CB1 inverse agonist

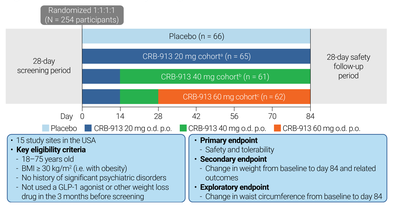


CB1, cannabinoid receptor type 1

METHODS

- CANYON-1 (NCT07310901) was a phase 1b, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study.
- The study design is shown in **Figure 2**.

Figure 2. CANYON-1 study design



Indicated days reflect planned visits. Actual participant visits were allowed up to 2 days before or after the planned visit day. [a]Received CRB-913 20 mg o.d. p.o. from day 0 to day 84. [b]Received CRB-913 20 mg o.d. p.o. from day 0 to day 13 then CRB-913 40 mg o.d. p.o. from day 14 to day 84. [c]Received CRB-913 20 mg o.d. p.o. from day 0 to day 13, then CRB-913 40 mg o.d. p.o. from day 14 to day 27, then CRB-913 60 mg o.d. p.o. from day 28 to day 84. BMI, body mass index; GLP-1, glucagon-like peptide-1 receptor; o.d., once daily; p.o., orally.

- Safety endpoint data were analyzed from the safety set and are presented as counts and percentages for categorical data, and means and standard errors of the mean for continuous data.
  - The safety set included all randomized participants who received at least one dose of the investigational drug.
- Efficacy endpoint (efficacy estimand) data were analyzed from the full analysis set using a mixed model for repeated measures with sex, randomized treatment group, visit and randomized treatment group-by-visit interaction as categorical fixed effects, and baseline weight as a covariate.
  - The full analysis set included all randomized participants who received at least one dose of the investigational drug.

RESULTS

Demographics and baseline characteristics of participants in CANYON-1

- In total, 254 participants were enrolled from 15 sites in the USA.
- Participant demographics and baseline characteristics are shown in **Table 1**.

Table 1. Participant demographics and baseline characteristics

Demographic or characteristic	Placebo (n = 66)	CRB-913 20 mg cohort[a] (n = 65)	CRB-913 40 mg cohort[b] (n = 61)	CRB-913 60 mg cohort[c] (n = 62)	Total (N = 254)
Age, years, mean (SD)	44.3 (14.2)	48.8 (12.2)	49.1 (12.4)	49.5 (13.5)	47.9 (13.2)
Sex, n (%)					
Female	46 (69.7)	45 (69.2)	44 (72.1)	45 (72.6)	180 (70.9)
Male	20 (30.3)	20 (30.8)	17 (27.9)	17 (27.4)	74 (29.1)
Race, n (%)					
White	36 (54.5)	44 (67.7)	40 (65.6)	47 (75.8)	167 (65.7)
Black or African American	24 (36.4)	20 (30.8)	19 (31.1)	11 (17.7)	74 (29.1)
Asian	2 (3.0)	0 (0.0)	0 (0.0)	2 (3.2)	4 (1.6)
Other	4 (6.1)	1 (1.5)	2 (3.3)	2 (3.2)	9 (3.5)
Weight, kg, mean (SD)	104.2 (19.7)	104.0 (25.0)	106.9 (20.3)	105.7 (22.2)	105.2 (21.8)
Body mass index, kg/m², mean (SD)	37.1 (5.1)	37.6 (6.8)	38.0 (5.0)	37.2 (5.7)	37.5 (5.7)
Waist circumference, cm, mean (SD)	113.0 (13.4)	112.5 (17.6)	115.1 (14.4)	113.8 (15.4)	–

[a]Received CRB-913 20 mg o.d. p.o. from day 0 to day 84. [b]Received CRB-913 20 mg o.d. p.o. from day 0 to day 13 then CRB-913 40 mg o.d. p.o. from day 14 to day 84. [c]Received CRB-913 20 mg o.d. p.o. from day 0 to day 13, then CRB-913 40 mg o.d. p.o. from day 14 to day 27, then CRB-913 60 mg o.d. p.o. from day 28 to day 84. o.d., once daily; p.o., orally; SD, standard deviation.

Safety of CRB-913 in participants with obesity

- A summary of primary endpoint safety data is shown in **Table 2**.
- Overall, 21 participants (8.3%) discontinued treatment early owing to adverse events (**Table 2**); 10 participants (3.9%) and 3 participants (1.2%), respectively, discontinued treatment owing to psychiatric or gastrointestinal adverse events. Discontinuations occurred in the CRB-913 cohorts and in the placebo cohort (**Table 2**).
- Psychiatric treatment-emergent adverse events (TEAEs) occurred both in the CRB-913 cohorts and the placebo cohort and were mild or moderate in severity, with no severe or serious psychiatric TEAEs reported (**Table 2**).
- Gastrointestinal TEAEs were mild or moderate in severity, with no severe or serious gastrointestinal TEAEs reported (**Table 2**).
- Overall, 10 participants (3.9%) discontinued treatment owing to psychiatric TEAEs (**Table 3**).
  - 6 of the 10 participants had concurrent nonpsychiatric TEAEs (e.g. gastrointestinal disorders, headache, pain).
  - 2 of the 10 participants had a history of anxiety.
  - 1 participant who received placebo who had no weight loss during the study or prior history of anxiety, discontinued owing to moderate anxiety.

Table 2. Summary of CRB-913 safety

	Placebo (n = 66)	CRB-913 20 mg cohort[a] (n = 65)	CRB-913 40 mg cohort[b] (n = 61)	CRB-913 60 mg cohort[c] (n = 62)	Total (N = 254)
Any TEAE, n (%)	28 (42.4)	39 (60.0)	45 (73.8)	45 (72.6)	157 (61.8)
Severe TEAE	0 (0.0)	3 (4.6)	2 (3.3)	1 (1.6)	6 (2.4)
Severe psychiatric TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe gastrointestinal TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious TEAE	0 (0.0)	2 (3.1)	1 (1.6)	1 (1.6)	4 (1.6)
Any TRAE, n (%)	14 (21.2)	27 (41.5)	34 (55.7)	33 (53.2)	108 (42.5)
Severe TRAE	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.4)
Serious TRAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment discontinuation for any reason, n (%)	12 (18.2)	10 (15.4)	16 (26.2)	16 (25.8)	54 (21.3)
Treatment discontinuation due to adverse event, n (%)	3 (4.5)	2 (3.1)	8 (13.1)	8 (12.9)	21 (8.3)

[a]Received CRB-913 20 mg o.d. p.o. from day 0 to day 84. [b]Received CRB-913 20 mg o.d. p.o. from day 0 to day 13 then CRB-913 40 mg o.d. p.o. from day 14 to day 84. [c]Received CRB-913 20 mg o.d. p.o. from day 0 to day 13, then CRB-913 40 mg o.d. p.o. from day 14 to day 27, then CRB-913 60 mg o.d. p.o. from day 28 to day 84. o.d., once daily; p.o., orally; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Table 3. Treatment discontinuation due to psychiatric TEAEs by assigned cohort and by dose at the time of adverse event occurrence

	Placebo (n = 66)	CRB-913 20 mg cohort[a] (n = 65)	CRB-913 40 mg cohort[b] (n = 61)	CRB-913 60 mg cohort[c] (n = 62)	Total (N = 254)
By assigned cohort, n (%)	1 (1.5)	1 (1.5)	3 (4.9)	5 (8.1)	10 (3.9)
By dose at time of adverse event occurrence,[d] n	1	3	2	4	10

[a]Received CRB-913 20 mg o.d. p.o. from day 0 to day 84. [b]Received CRB-913 20 mg o.d. p.o. from day 0 to day 13 then CRB-913 40 mg o.d. p.o. from day 14 to day 84. [c]Received CRB-913 20 mg o.d. p.o. from day 0 to day 13, then CRB-913 40 mg o.d. p.o. from day 14 to day 27, then CRB-913 60 mg o.d. p.o. from day 28 to day 84. [d]To account for the dose escalation protocol, adverse event numbers reflect the actual dose participants were receiving at the time the event occurred. o.d., once daily; p.o., orally; TEAE, treatment-emergent adverse event.

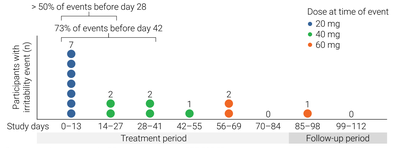
  - None of the discontinuations were due to irritability, which was listed as a concomitant adverse event in 2 participants who discontinued owing to other psychiatric TEAEs.
  - Half of the discontinuations due to psychiatric TEAEs occurred before day 42 and none occurred after day 70.
- Irritability was the most frequently reported psychiatric TEAE. Anxiety, depression and insomnia occurred infrequently and there were no instances of suicidal ideation reported in any of the cohorts during the study (including follow-up) (**Table 4**).
- All psychiatric TEAEs were resolved, and most participants continued treatment.
- Overall, 15 participants experienced irritability during the study (**Figure 3**).
  - All instances of irritability were mild and resolved, and participants reported no impact on daily function.
  - 12 of the 15 participants had concomitant nonpsychiatric adverse events (e.g. gastrointestinal disorders, migraine, ear infection).
  - All 15 reported instances of irritability coincided with weight loss.
  - Greater than 50% of irritability events occurred before day 28 and 73% occurred before day 42.

Table 4. Important psychiatric TEAEs

Adverse event of special interest	Placebo (n = 66)	CRB-913 20 mg cohort[a] (n = 65)	CRB-913 40 mg cohort[b] (n = 61)	CRB-913 60 mg cohort[c] (n = 62)	Total (N = 254)
Irritability	0 (0.0)	4 (6.2)	5 (8.2)	6 (9.7)	15 (5.9)
Anxiety	3 (4.5)	2 (3.1)	5 (8.2)	3 (4.8)	13 (5.1)
Insomnia	2 (3.0)	1 (1.5)	3 (4.9)	0 (0.0)	6 (2.4)
Depressive symptoms	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.4)
Suicidality	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a]Received CRB-913 20 mg o.d. p.o. from day 0 to day 84. [b]Received CRB-913 20 mg o.d. p.o. from day 0 to day 13 then CRB-913 40 mg o.d. p.o. from day 14 to day 84. [c]Received CRB-913 20 mg o.d. p.o. from day 0 to day 13, then CRB-913 40 mg o.d. p.o. from day 14 to day 27, then CRB-913 60 mg o.d. p.o. from day 28 to day 84. o.d., once daily; p.o., orally; TEAE, treatment-emergent adverse event.

Figure 3. Irritability adverse events by dose at the time of adverse event occurrence



Doses by assigned cohort: the 20 mg cohort received CRB-913 20 mg o.d. p.o. from day 0 to day 84; the 40 mg cohort received CRB-913 20 mg o.d. p.o. from day 0 to day 13 then CRB-913 40 mg o.d. p.o. from day 14 to day 84; and the 60 mg cohort received CRB-913 20 mg o.d. p.o. from day 0 to day 13, then CRB-913 40 mg o.d. p.o. from day 14 to day 27, then CRB-913 60 mg o.d. p.o. from day 28 to day 84. o.d., once daily; p.o., orally.

- Treatment discontinuation due to gastrointestinal TEAEs occurred in 3 participants (2 who received CRB-913 and 1 who received placebo).
- Diarrhea was the most frequent gastrointestinal TEAE (**Table 5**).
- Half of the diarrhea TEAEs and 60% of the nausea TEAEs occurred by day 14.

Efficacy of CRB-913 in participants with obesity

- As early as day 14, all CRB-913 dose cohorts showed significant ($p < 0.0001$) weight loss compared with baseline (**Figure 4**). No significant weight loss was observed with placebo at any time point in the study.
- On day 84, significant ($p < 0.0001$) dose-dependent weight loss from baseline was observed with CRB-913 but not placebo. The CRB-913 60 mg cohort had a placebo-adjusted least-squares mean weight change of −5.0% (standard error of the mean, 0.59; **Figure 4**).

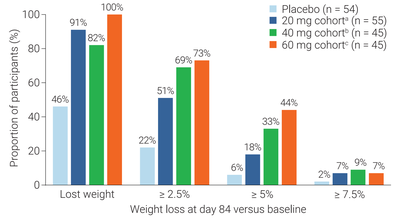
Table 5. Important gastrointestinal TEAEs

Adverse event of special interest	Placebo (n = 66)	CRB-913 20 mg cohort[a] (n = 65)	CRB-913 40 mg cohort[b] (n = 61)	CRB-913 60 mg cohort[c] (n = 62)	Total (N = 254)
Diarrhea	2 (3.0)	14 (21.5)	16 (26.2)	14 (22.6)	46 (18.1)
Nausea	3 (4.5)	10 (15.4)	16 (26.2)	14 (22.6)	43 (16.9)
Vomiting	0 (0.0)	3 (4.6)	5 (8.2)	1 (1.6)	9 (3.5)
Constipation	2 (3.0)	3 (4.6)	1 (1.6)	3 (4.8)	9 (3.5)

[a]Received CRB-913 20 mg o.d. p.o. from day 0 to day 84. [b]Received CRB-913 20 mg o.d. p.o. from day 0 to day 13 then CRB-913 40 mg o.d. p.o. from day 14 to day 84. [c]Received CRB-913 20 mg o.d. p.o. from day 0 to day 13, then CRB-913 40 mg o.d. p.o. from day 14 to day 27, then CRB-913 60 mg o.d. p.o. from day 28 to day 84. o.d., once daily; p.o., orally; TEAE, treatment-emergent adverse event.

- On day 84, all participants in the 60 mg cohort had weight loss compared with baseline; 44% had a weight loss of at least 5% compared with baseline (**Figure 5**).
- Similar weight loss profiles were observed for female and male participants in all CRB-913 treatment groups.
- Participants treated with CRB-913 also experienced dose-dependent reductions in waist circumference and body mass index during the study period.

Figure 5. A greater proportion of participants who received CRB-913 lost weight than those who received placebo

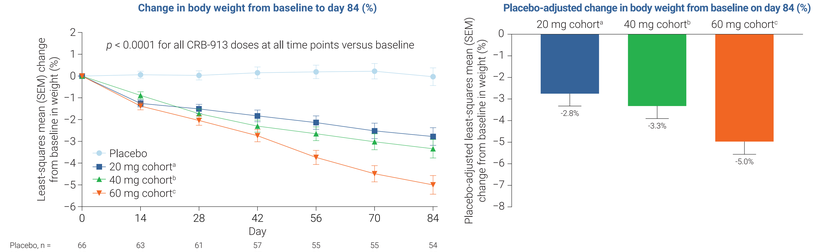


[a]Received CRB-913 20 mg o.d. p.o. from day 0 to day 84. [b]Received CRB-913 20 mg o.d. p.o. from day 0 to day 13 then CRB-913 40 mg o.d. p.o. from day 14 to day 84. [c]Received oral CRB-913 20 mg o.d. p.o. from day 0 to day 13, then CRB-913 40 mg o.d. p.o. from day 14 to day 27, then CRB-913 60 mg o.d. p.o. from day 28 to day 84. o.d., once daily; p.o., orally.

Our findings in context

- Participants in the CRB-913 60 mg cohort had similar weight loss at 12 weeks to those reported for oral glucagon-like peptide-1 receptor (GLP-1) agonists in previously published studies (**Table 6**).[3–5]

Figure 4. CRB-913 produced dose-dependent weight loss by day 84 with no evidence of plateauing



Placebo, n =	66	63	61	57	55	55	54
20 mg cohort, n =	65	63	61	57	56	56	55
40 mg cohort, n =	61	61	60	54	51	48	45
60 mg cohort, n =	62	56	55	53	52	48	45

*p < 0.0001 for placebo-adjusted change in body weight from baseline on day 84. [a]Received CRB-913 20 mg o.d. p.o. from day 0 to day 84. [b]Received CRB-913 20 mg o.d. p.o. from day 0 to day 13 then CRB-913 40 mg o.d. p.o. from day 14 to day 84. [c]Received CRB-913 20 mg o.d. p.o. from day 0 to day 13, then CRB-913 40 mg o.d. p.o. from day 14 to day 27, then CRB-913 60 mg o.d. p.o. from day 28 to day 84. o.d., once daily; p.o., orally; SEM, standard error of the mean.

Table 6. At 12 weeks, CRB-913 demonstrated similar weight loss to that seen with oral GLP-1 agonists

	Change in weight compared with baseline (%)		
	4 weeks	8 weeks	12 weeks
Oral semaglutide 25 mg[3]	−1.1	−2.6	−4.3
Orforglipron 17.2 mg[4,5]	−1.4	−3.1	−4.5
CRB-913 60 mg	−2.1	−3.9	−5.0

These limited observations are derived from separate clinical settings and are not head-to-head comparisons.
For orforglipron, early clinical development evaluated a 36 mg capsule formulation; subsequent bridging established pharmacokinetic bioequivalence to the 17.2 mg tablet commercial formulation. Weight loss data at 12 weeks were taken from published data from a 68-week study for oral semaglutide and a 36-week study for orforglipron. GLP-1, glucagon-like peptide-1 receptor.

CONCLUSIONS

- CRB-913 was well tolerated with a favorable safety profile in participants with obesity who were treated for 12 weeks.
- Psychiatric TEAEs were infrequent and mostly mild in severity, with no instances of suicidal ideation or behavior observed and no serious or severe psychiatric TEAEs of any kind reported in any treatment group.
  - Rates of depression, anxiety and insomnia were broadly in line with data published for incretin analogs.
  - Instances of irritability were all mild in severity and appeared treatment-related. Psychiatric adverse events generally occurred early in the study and were all resolved.
- Although no direct head-to-head comparisons have been performed, rates of vomiting, nausea and constipation were lower with CRB-913 than those previously published for oral GLP-1 agonists. Rates of diarrhea in the present study appear to be in line with published data for oral GLP-1 agonists.
- CRB-913 demonstrated promising efficacy data with significant weight loss compared with baseline occurring within 15 days of treatment initiation.
- In the CRB-913 60 mg cohort, all participants who completed treatment lost weight, with a mean reduction of 5.0% on day 84 and no evidence of the effect plateauing at the end of the study.
- In the 60 mg cohort, participants had weight loss at 12 weeks that was similar to that of GLP-1 agonist treatment reported by previously published studies.[3–5]
- These data support the potential of CRB-913 as a non-incretin-based oral therapy for obesity.

References

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PRESENTING AUTHOR DISCLOSURES

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