Commentary on a Clinical Trial: Cannabinoid antagonist in obesity treatment

Cannabinoid antagonist in obesity treatment

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Clinical design
The overall clinical development plan of CP-945.598 was to demonstrate clinically significant weight loss and improvement in obesity-related comorbid illnesses (type 2 diabetes mellitus, hypertension and dyslipidaemia) with a safety and tolerability profile that is appropriate for long-term therapy. Phase 1 studies addressed safety, tolerance, pharmacokinetics and potential for drug-drug interactions. A Phase 2a six-week study demonstrated a good safety and toleration profile over this period of administration and reduced food intake in overweight patients (BMI > 27 kg/m²) with hypertension or dyslipidaemia also demonstrating a good safety and toleration profile and clinically and statistically significant weight loss over six months of administration. In Phase 3, studies were conducted per published regulatory guidelines to characterise long-term efficacy and safety in target patient populations.

In humans, orally administered CP-945.598 has a moderate rate of oral absorption (tablet tmax = 4 to 6 hours) and a terminal phase half-life (~ 107 to 163 hours). Steady-state exposures increase approximately dose-proportionally over 5 to 25 mg QD, but less than dose-proportionally at > 50 mg, with essentially similar exposures at 100 and 200 mg QD as a result of apparent dose-dependent auto-induction. Fluctuation in steady-state exposure over the dosing interval is low, with peak-to-trough ratios of approximately 1.4 to 2.5 at 5 to 25 mg QD doses in obese subjects.

Based on preliminary results of a PK/PD (pharmacokinetic/pharmacodynamic) analysis of weight loss in the Phase 2b study, clinically meaningful weight loss (≥ 5% placebo-adjusted per cent weight loss) was likely to be achieved following one year of treatment with 20 to 25 mg doses of CP-945.598. CP-945.598 was unlikely to produce clinically relevant QT prolongation over the clinical dose range (≤ 25 mg QD) based on the results of a population PK/QT analysis on pooled Phase 1 data.

The 25 mg dose was considered the upper end of the dose range for the Phase 2 and 3 studies due to clinically significant CYP3A induction (and auto-induction) at higher doses. Based on the results of the six-week Phase 2a study, a mean steady-state (Cmax of ~ 69.4 ng/mL) was observed at the maximum recommended human dose of 25 mg. For the purpose of comparing the effects observed at other exposures in nonclinical and clinical studies, the mean steady-state Cmax of ~ 69.4 ng/mL was used as reference.

Mechanism of action
Blocking the action of CB1 receptors would be expected to have beneficial effects by reducing food intake, increasing adiponectin, reducing the storage of fat and improving glucose uptake and oxygen consumption in muscle, thereby increasing satiety. (See Table I.)

Circulating endocannabinoid levels in the blood of lean and obese humans are demonstrated in Figure 1. Obese humans have significantly more AEA and significantly more 2-AG. In obesity, this

Table I: Multisite impact of CB1 receptor blockade on metabolism

| Site of action            | Mechanism(s)       | Clinical implications                  |
|---------------------------|--------------------|----------------------------------------|
| Hypothalamus/Nucleus ac-cumbens | ↓ Food intake       | • Weight loss, reduced waist circumference |
| Adipose tissue            | ↑ Adiponectin Lipogenesis | • Reduced visceral fat • Improved lipidaemia • Insulin sensitivity |
| Muscle                    | ↑ Glucose uptake O₂ consumption | • Insulin sensitivity |
| Liver                     | ↓ Lipogenesis       | • Improved lipidaemia • Insulin sensitivity |
| GI tract                  | ↓ Satiety           | • Weight loss |

Introduction
CP-945.598 is an orally active selective antagonist of the cannabinoid CB-1 receptor that has been developed for weight loss and the prevention of weight regain in obese and overweight individuals.
system is turned off significantly and presumably contributes to all of the cardiometabolic problems associated with obesity.

**Summary**

At the time of this study, the overall clinical experience with this compound was positive. Based on the pharmacologic properties of CP-945,598, the toxicological findings and observations from the human studies performed to date, the primary potential side-effects in humans are nausea, vomiting, diarrhoea, loose stools, dizziness, headache, hiccups, abdominal pain, fatigue, insomnia, somnolence, pruritis and decreased appetite. Suicidal thoughts and behaviour (suicidality) have been reported for another CB1 antagonist (rimonabant), a compound that is currently approved in 37 countries, but not in the United States of America. In July 2007, upon review of additional safety information, The European Medicines Agency recommended Acomplia (rimonabant) not be used in patients with ongoing major depression or taking antidepressants because of the risk of psychiatric side-effects. The Committee for Medicinal Products for Human Use also added a warning that treatment with rimonabant should be stopped if a patient developed depression.

Psychiatric adverse events, including depression, depressed mood, anxiety and suicidal ideation have been reported with CP-945.598. Psychiatric adverse effects, including depression and suicidality, were being monitored, assessed and followed up appropriately as per protocol in studies with CP-945.598.

In-vitro assessment of the phototoxic potential of CP-945.598 was positive, indicating the potential for CP-945.598 to cause photodamage and/or phototoxicity in tissues. The results of a designated clinical photosensitivity study A5351016 suggest that CP-945.598 is not likely to be a clinically meaningful phototoxic agent based on the negative primary endpoint of delayed photosensitivity.

In addition, there have been no adverse events reported from completed or ongoing clinical studies that suggest that CP-945.598 causes a clinically significant phototoxic effect.

Two ongoing two-year studies in obese subjects and a one-year study in obese type 2 diabetic subjects were terminated recently due to the observed side-effect profile.

**Reference**

1. Janero DR, Makriyannis A. Cannabinoid receptor antagonists: Pharmacological opportunities, clinical experience, and translational prognosis. Expert Opin Emerg Drugs. 2009 Mar;14(1):43-65.

Figure 1: The endocannabinoid system is upregulated in human obesity

![Circulating endocannabinoid levels are higher in obese vs lean women](Image)

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