Cannabinoid Receptor Agonist 13, a Novel Cannabinoid Agonist: First in Human Pharmacokinetics and Safety

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ABSTRACT:
Cannabinoid receptor agonist 13 (CRA13) is a novel cannabinoid (CB) receptor agonist with high affinity and functional activity toward both CB1 and CB2 receptors. This phase I study aimed to evaluate the pharmacokinetics, safety, and tolerability of single oral doses of CRA13. Sixty-three of 69 healthy adult males were randomized in seven cohorts (n = 9) to receive 1 to 80 mg of CRA13 or placebo orally in fasted condition. To investigate the diet effect, an independent group (n = 6) was randomized to receive 40 mg of CRA13 after high-fat and high-calorie breakfast in crossover design with a 2-week washout period. Peak plasma concentration (Cmax) ranged from 7.8 to 467.6 ng/ml (1–80 mg). CRA13 was rapidly absorbed and demonstrated linear pharmacokinetics (1–80 mg). Time to reach Cmax (tmax) was 1.5 to 2 h for all doses in both fasted and fed groups. Administration of 40 mg of CRA13 with food induced approximately 2-fold increase in the Cmax and the area under the concentration-time curve, AUC0–tz. The apparent elimination half-life (t1/2) was 21 to 36 h and 30 to 41 h for fasted and fed groups, respectively. Dizziness, headache, and nausea were the most frequently reported adverse events (AEs), predominantly at the 40- and 80-mg doses. The incidence of AEs was dose-dependent and mild to moderate. No deaths and serious adverse events were reported. In conclusion, CRA13 was reasonably well tolerated and demonstrated a linear pharmacokinetics over the studied dose range (1–80 mg). Food intake increased CRA13 Cmax and AUC0–tz by approximately 2-fold, whereas tmax was unaffected.

Cannabinoid receptor agonist 13 (CRA13) is a novel cannabinoid (CB) receptor agonist with high affinity and functional activity toward both CB1 and CB2 receptors (Dziadulewicz et al., 2007). Cannabis extracts contain a mixture of psychoactive, highly brain-penetrant cannabinoids, structurally related to the major active constituent Δ9-tetrahydrocannabinol (Fig. 1). In animals, cannabinoids are known to produce a range of well established effects including analgesia, catalepsy, reduced locomotor activity, and hypothermia. These effects are mediated through the activation of CB1 and CB2 receptors, both of which are G-protein-coupled and exert their effects predominantly via inhibition of adenylate cyclase (Pertwee and Ross, 2002). Published literature indicates that CB agonists may also be effective against persistent nociceptive processes in clinical conditions associated with chronic pain states (Richardson, 2000; Fox et al., 2001; Pertwee, 2001; Rice, 2001; Karst et al., 2003; Notcutt et al., 2004; Svendsen et al., 2004).

Selective activation of peripheral CB1 receptors could evolve as a valuable therapy for chronic pain conditions as long as the central nervous system (CNS) effects are suppressed. CRA13, in behavioral animal models (rat and guinea pig) of chronic pain (neuropathic and nociceptive), was able to reverse established mechanical hyperalgesia after both oral administration and local injection into hind-paw. In behavioral tests for CNS activity in rat, CRA13 produced significant CNS effects only at doses that were 20-fold higher than the oral doses required to reverse hyperalgesia. Thus, these data indicate that CRA13 produces antihyperalgesic activity predominantly via an action on peripheral sensory nerves.

The in vitro selectivity of CRA13 in 61 receptor and ion channel assays showed no significant binding up to a concentration of 10 μM and had a weak affinity for the guinea pig histamine H1 receptor (pKᵢ ~ 5.8), which is unlikely to cause any pharmacological side effects (Dziadulewicz et al., 2007). The results suggest that side effects associated with activation or inhibition of these receptors can be excluded in all probability.

In vivo pharmacokinetics of CRA13 after a single intravenous dose (1 mg/kg) and a single oral dose (3.4 and 1 mg/kg in rat and dog, respectively) have been investigated in Wistar rats and Beagle dogs. After oral administration CRA13 was rapidly absorbed [time to reach peak plasma concentration (Cmax) (tmax), 1–2 h]. A good absorption was observed in rat (57%) and dog (74%). The absolute bioavailability amounted to 43 and 14% in rat and dog, respectively, indicating an important presystemic first pass in dog. The terminal half-life (t1/2) of CRA13 was 64.6 and 10.7 h in rat and dog, respectively (A. Gardin, unpublished observations, data on Novartis file).

In safety pharmacology studies in telemetered dogs, 3 mg/kg CRA13 p.o. caused no significant effects on the cardiovascular sys-
In 2-week oral toxicity studies, CRA13 was well tolerated at doses up to 3 mg/kg in rats and dogs. The maximum nonlethal intravenous dose was 20 mg/kg in mice and 50 mg/kg in rats (K. Kucher, unpublished observations, data on Novartis file).

Because CRA13 has shown an acceptable safety profile in animal toxicity and cardiovascular safety studies, it was justifiable to evaluate its safety and therapeutic potential in humans. The purpose of this first-in-man study was to investigate acute safety, tolerability, and pharmacokinetics of CRA13 after oral administration of single ascending doses (1–80 mg) and to assess the effect of food on the pharmacokinetics of CRA13.

### Materials and Methods

#### Study Design

This was a randomized, double-blind, placebo-controlled, time-lagged, parallel-group (seven groups of nine subjects), ascending single oral-dose study. The effect of food on the pharmacokinetics of CRA13 was investigated in an additional group of six subjects using a single-dose, randomized, two-way, crossover design with a washout period of a minimum of 2 weeks.

The study was conducted at Covance Clinical Research Unit (Leeds, UK) in accordance with the standards for Good Clinical Practices (Food and Drug Administration, 1996) and the Principles of the Declaration of Helsinki (World Medical Association, 2000). The protocol was approved by the Covance Clinical Research Unit Independent Review Board (Leeds, UK).

#### Study Population

A total of 69 (63 male) healthy, white, male subjects aged between 18 and 45 years were included in the study. For all subjects, body weight was within ±15% normal for their height and frame size. Frame size was determined using elbow breadth measurement (medium frame was defined as elbow breadth between 6.4 and 8.1 cm for height from 158 to 193 cm for males and between 5.6 and 6.9 cm for height from 148 to 183 cm for females) (Metropolitan Life Insurance Company, 1983). All volunteers provided written, informed consent before enrollment. All were in good health as evidenced by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests (hematology, biochemistry, and urinalysis) performed within 21 days before commencement of the study.

Subjects who had donated or lost 400 ml or more of blood within 8 weeks before the study and with a history of significant illness within 2 weeks before the study were not eligible to participate. In addition, those with a history of clinically significant electrocardiogram (ECG) abnormalities or a family his-

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**FIG. 1. Proposed metabolic pathways of CRA13 in liver microsomal incubates.**
tory of prolonged QT interval syndrome, autonomic dysfunction, history of acute or chronic bronchopulmonary disease (including asthma and chronic obstructive pulmonary disease), or history of clinically significant drug allergy, atopic allergy, or a known hypersensitivity to the study drug or similar drugs were not eligible. All included volunteers were nonsmokers. Subjects were screened for drugs of abuse and cotinine and hepatitis B/C and HIV infection. Except for medication required to treat adverse events (AEs), no medication other than the study drug was allowed from 14 days before dosing until all of the final study evaluations had been completed. Administration of paracetamol was acceptable.

**Dosage and Treatment.** Subjects were assigned a subject number corresponding to the randomization number according to a predetermined randomization schedule. After an overnight fast of 10 h, subjects were randomly assigned to receive CRA13 (1, 2.5, 5, 10, 20, 40, or 80 mg) or placebo. CRA13 was administered as a micellar solution consisting of CRA13 dissolved in Cremophor RH40, propylene glycol, and Labrafir M 2125 CS. The concentrate (104.3 mg/ml) was diluted with 150 ml of deionized water before dosing. In each group, six of the nine subjects were randomized to receive CRA13, and three were randomized to receive placebo. All volunteers continued to fast for an additional 4 h postdose, when lunch was served.

**Food effect.** After an overnight fast of 10 h, the subjects received high-fat and high-calorie breakfast (consisting of two eggs fried in oil, two strips of bacon, one slice of white toast with 10 g butter, two hash brown potatoes, 240 ml of half-fat milk) as per Food and Drug Administration recommendations (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, 2002) and then received single doses of 40 mg of CRA13 within 10 min after completeing breakfast.

The intake of methylxanthine-containing food or beverages (e.g., caffeine) and alcohol was restricted, and unless performing a study assessment, subjects had to rest quietly in the upright position for 4 h after dose administration. There was a subsequent observation period of 96 h.

**Sampling Schedule.** Blood samples were drawn from a forearm vein 30 min before dosing and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 h after drug administration. Blood samples were collected into a lithium heparin tube, by either direct venipuncture or an indwelling cannula. The samples were centrifuged under refrigeration (3–5°C) for 15 min at approximately 1500g. The plasma was transferred into polypropylene screw-cap tubes and stored at ≤–18°C until the time of analysis.

**Pharmacokinetic Assessment.** Analytical method for measurement of plasma concentrations of CRA13. CRA13 plasma samples were subjected to protein precipitation followed by liquid chromatography-tandem mass spectrometry analysis using atmospheric pressure chemical ionization in positive ion mode.

The assay had a lower limit of quantification (LLOQ) of 1.77 ng/ml and was validated from 2 to 500 ng/ml. At LLOQ, the interday accuracy and precision were 97.5 and 10.6%, respectively. Above LLOQ, the interday accuracy and precision were evaluated by standard noncompartmental methods using WinNonlin Pro Software. The assay had a lower limit of quantification (LLOQ) of 1.77 ng/ml and was validated from 2 to 500 ng/ml. At LLOQ, the interday accuracy and precision were 97.5 and 10.6%, respectively. Above LLOQ, the interday accuracy and precision were evaluated by standard noncompartmental methods using WinNonlin Pro Software.

Pharmacokinetic parameters. Plasma CRA13 concentration-time profiles were evaluated by standard noncompartmental methods using WinNonlin Pro version 4.0 (Pharsight, Mountain View, CA). Plasma concentrations below the limit of quantification were considered 0 in all calculations. The $C_{\text{max}}$ and the $t_{\text{max}}$ were recorded from experimental observations. The elimination phase rate constant ($k_e$) and its corresponding half-life ($t_{\text{1/2}}$), calculated as ln 2/$k_e$, were derived from the log-linear terminal slope of the plasma concentration-time profile by least-squares linear regression analysis. Area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration ($AUC_{0-\text{last}}$) was calculated using the linear trapezoidal method with $AUC_{0-\text{last}}$ computed as $AUC_{0-\text{last}}$ plus the extrapolation from the last quantifiable time point to infinity using $C/\beta$, where $C_{\text{1/2}}$ represents the last quantifiable concentration.

**Statistical Analysis.** Fasting subjects receiving active treatment in the seven dose-escalation groups or in period 1 of the fasting/fed cohort were included in the dose proportionality analysis. Fasting subjects in period 2 of the fasting/fed cohort were also included if there were no significant period effects found during the crossover analysis of this cohort. The following model was fitted using PROC MIXED in SAS version 8.2 (SAS Institute, Cary, NC): $\text{Ln}(\text{PK variable}) = \text{Ln}(a) + b \times \text{Ln}(\text{Dose})$, where PK is pharmacokinetics.

The model was fitted to the following pharmacokinetic variables: $C_{\text{max}}$ and $AUC_{0-\text{last}}$. The 95% confidence interval (CI) for the slope $b$ was estimated to judge the degree of dose proportionality. To test the appropriateness of the power model, a lack-of-fit test was performed: $\text{Ln}(\text{PK variable}) = \text{Ln}(a) + b \times \text{Ln}(\text{Dose}) + Dose$, where Dose represents the lack-of-fit test. If the lack-of-fit test was found to be significant at the 5% level, then evidence of dose proportionality could not be inferred. In the case where the lack-of-fit test was not statistically significant, the power model was fitted.

To assess the effect of food on the pharmacokinetics of CRA13, a comparison of the pharmacokinetic variables ($C_{\text{max}}$ and $AUC_{0-\text{last}}$) between the fed and fasted groups was performed for the 40-mg dose using an analysis of variance model, with treatment, sequence, and period as fixed effect and subject within sequence as a random effect. From this analysis of variance, the estimated treatment differences were calculated and back-transformed to give the ratio (fed versus fasted) between the geometric food group means, together with the corresponding 90% CIs.

### Results

All 69 subjects (white origin) who were enrolled completed the study. There were no substantial differences between groups with respect to demographics (Table 1).

**Pharmacokinetics.** Single-dose pharmacokinetics. The absorption of CRA13 was rapid, and plasma concentrations were determined as early as 15 min after drug intake. $C_{\text{max}}$ values ranging from 7.8 to 467.6 ng/ml appeared 1.5 to 2 h after oral administration. Arithmetic mean plasma concentration-time profiles observed after administration of a single oral dose of CRA13 (1, 2.5, 5, 10, 20, 40, and 80 mg) to fasted subjects are shown in Fig. 2.

Exposure to CRA13 ($C_{\text{max}}$ and $AUC_{0-\text{last}}$) increased with dose and showed an essentially linear relationship as indicated by correlation coefficients of 0.908 and 0.899 for $C_{\text{max}}$ and $AUC_{0-\text{last}}$, respectively (Fig. 3). However, dose proportionality could not formally be established by the statistical analysis. There was a slight trend for under-proportionality for $C_{\text{max}}$ (95% CI, 0.849 to 0.979) and a slight tendency for overproportionality for $AUC_{0-\text{last}}$ (95% CI, 1.044 to 1.225), although estimates were close to 1. The intersubject variabilities with respect to $C_{\text{max}}$, $AUC_{0-\text{last}}$, and $AUC_{0-\text{last}}$ (percentage coefficient of variation in geometric mean) were on average in the range of 16 to 45, 26 to 66, and 25 to 45%, respectively, across the doses studied. The derived pharmacokinetic parameters are provided in Table 2. The apparent terminal half-lives ranged, on average, between 21 and 34 h.

**Food effect.** The mean plasma concentration-time profiles in the fed/fasted stage are shown in Fig. 4. The $C_{\text{max}}$ and $AUC_{0-\text{last}}$ after administration of 40 mg with food were 369 ng/ml and 3015 ng/h/ml, respectively. $t_{\text{max}}$ was found to be independent of food effect and was on average 2 h postdose. The intersubject variability in the pharmacokinetic parameters was of similar magnitude under both dosing conditions (Table 3).

### Table 1

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Mean (n = 69)</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>179.3 ± 6.7</td>
<td>169</td>
<td>193</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.6 ± 8.3</td>
<td>55.3</td>
<td>90</td>
</tr>
<tr>
<td>Elbow breadth (cm)</td>
<td>7.3 ± 0.3</td>
<td>6.5</td>
<td>8.0</td>
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</table>
Safety and Tolerability. Adverse events. Eighteen of the 48 (38%) subjects treated with CRA13 experienced a total of 52 AEs, and three of the 21 (14%) placebo subjects reported four AEs. There was a dose-dependent increase in the incidence of AEs. The highest incidence was seen with the dose of 80 mg fasted, followed by the dose of 40 mg coadministered with food. The number and, in individual cases, severity of AEs after 40-mg fed administration (mild, 18; moderate, one; severe, one) was higher than that with fasted administration (mild, six) in the same subjects.

No case of death or serious adverse event was reported, and most AEs were mild to moderate in severity. Dizziness, headache, and nausea were the most frequently reported AEs. Dizziness was reported by six subjects on CRA13 (one at 10 mg, one at 20 mg, one at 40 mg fed, three at 80 mg). Five subjects reported headache (one in 20 mg, two in 40 mg, two in the 40-mg fasted/fed cohort, one in the fed state, and one in the fasted state). Somnolence was reported only in three subjects that received 40 mg fasted/fed. Four episodes of tiredness and lethargy were reported, thrice by one subject in the 40-mg group and once by a subject in the 80-mg CRA13 group. Most AEs resolved spontaneously without additional drug(s).

Vital signs and laboratory findings. Body temperatures of subjects did not show any deviation. However, most subjects showed isolated, minor deviations from the normal range for blood pressure and pulse. Orthostatic hypotension was observed in one patient (receiving 20 mg).

Most subjects showed isolated, minor deviations from the normal range for different hematology, blood chemistry, or urinalysis parameters at various time points during the study. None of these deviations were considered as clinically relevant, and no dose relationship was apparent. There was no QTc prolongation (QTc > 450 ms) observed during ECG tracings.

Discussion

The pharmacokinetics, safety, and tolerability of a single oral dose of CRA13 were investigated. CRA13 was rapidly absorbed, and $C_{\text{max}}$ was observed on average 2 h after drug administration in fed or fasted conditions. CRA13 showed an essentially linear relationship (1–80 mg). The 10-mg dose cohort seemed to be a deviation; however, dose linearity was assessed considering the whole range of dose levels, and Fig. 3a clearly shows that the geometric means fluctuated around the regression line. The 10-mg dose group appeared to be an outlier because the variability in $C_{\text{max}}$ was smaller (%CV geometric mean of 16%) than for other dose groups (%CV geometric mean between 23–45%). This might be a random effect due to the small sample size, and this observation was not confirmed with higher dose levels.

For most of the subjects, a slight plateau phase was observed between 4 and 6 h after administration. For some others, this phenomenon was more pronounced, and a double-peak emerged at approximately 6 h postdose. This might be due to enterohepatic recirculation of CRA13 because drugs subject to enterohepatic recirculation are often characterized by multiple peaks and a long half-life (e.g., estradiol) (Vree and Timmer, 1998). Likewise, compounds of many other classes such as sulfonamide diuretics (Vree and van der Ven, 1999), antiarrhythmic drugs (Freedman and Somberg, 1991), or nonsteroidal anti-inflammatory drugs (Busch et al., 1995) are also subjected to enterohepatic recirculation. In addition, the bile salts, released after meal ingestion, could have facilitated further dissolution and solubilization of CRA13 [solubility in water, $-$0.001–0.002 mg/ml; log partition coefficient (log P) = 6.9], allowing a second absorption phase. The plasma concentration-time profiles showed a steep increase until $t_{\text{max}}$, followed by a biphasic decrease, reflecting distribution and elimination phases. The terminal half-life ranged from 21 to 34 h and could only be determined for the higher dose groups (20–80 mg) because of sensitivity limitations of the bioanalytical method.

CRA13 is highly lipophilic and belongs to class II compounds (low solubility and high permeability) of the Biopharmaceutics Classification System. As a consequence of their poor solubility and dissolution in the gastrointestinal fluids, these compounds are incompletely absorbed. The high fat content of a coadministered meal and/or an increased secretion of bile salts after food intake may lead to an improved solubility and dissolution rate, consequently enhancing the extent of absorption (Lindholm et al., 1990; Charman et al., 1997). Therefore, in the present study, the effect of food on CRA13 pharmacokinetics was also evaluated. A 2-fold increase in $C_{\text{max}}$ and $\text{AUC}_{0-\infty}$ was observed after administration of CRA13 40 mg with a high-fat and high-calorie breakfast. Mean $C_{\text{max}}$ in the fasted period of the food effect cohort was lower (176.2 ng/ml) than the $C_{\text{max}}$ reported for the 40-mg dose group in the main part of the study (272.4 ng/ml).
However, it should be noted that these were two distinct subject groups and two low \( C_{\text{max}} \) values were observed in the food effect cohort after fasted administration. This might be a random effect considering the small sample size.

In addition, food consumption may also increase CRA13 intestinal uptake by prolonging the gastric residence time or by enhancing the mucosal permeability. CRA13 behaves in a manner similar to manidipine, another highly lipophilic (\( \log P = 5.18 \)) drug, because of which the food absorption improved significantly, with 25 and 50% increases in \( C_{\text{max}} \) and AUC, respectively, but with no effect on \( t_{\text{max}} \). The authors suggested that the increase in manidipine bioavailability was related to its lipophilicity and could be explained through a solubilization effect produced by food and bile secretions (Rosillon et al., 1998).

The absorption of many lipophilic compounds is enhanced by food, and it is likely that intestinal lymphatics transport plays a role in absorption under postprandial conditions (Gershkovich and Hoffman, 2007). The intestinal lymphatic transport contributes significantly to the amount absorbed from the gastrointestinal tract for the drugs that are associated with a high triglyceride solubility (\( \geq 50 \) mg/ml) and a \( \log P \) value in excess of 5 (Charman and Stella, 1986). CRA13, which exhibits an extremely high lipophilicity (\( \log P = 6.9 \)) and a good triglyceride solubility, fulfills these requirements. Despite the high rate of fluid transport in the intestinal lymphatics \([\sim 0.2\% (v/v)]\) compared with portal blood (Charman and Stella, 1992), a high-affinity binding of the lipophilic drugs to the lymph lipoproteins can provide a means for attaining high lymphatic drug concentrations and thereby contribute to bioavailability. In vitro protein-binding studies
Pharmacokinetics parameters after single administration of CRA13 to healthy subjects under fasted condition

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Dose</th>
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<tr>
<td></td>
<td>1 mg</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>$8.0 \pm 2.4$</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>[7.8; 29]</td>
</tr>
<tr>
<td>$t_{\text{lag}}$ (h)</td>
<td>0.25 (0.0–0.5)</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>N.A.</td>
</tr>
<tr>
<td>$AUC_{0\text{-}t_{\text{lag}}}$ (h/ng/ml)</td>
<td>29 ± 9</td>
</tr>
<tr>
<td>$AUC_{0\text{-}\infty}$ (h/ng/ml)</td>
<td>[28; 31]</td>
</tr>
<tr>
<td>$V_{\text{z/F}}$ (l)</td>
<td>N.A.</td>
</tr>
<tr>
<td>$V_{d/F}$ (l)</td>
<td>N.A.</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>N.A.</td>
</tr>
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CL/F, total body clearance (F is the fraction of dose absorbed); $V_{z/F}$, volume of distribution (F is the fraction of dose absorbed); N.A., not applicable.

$^a n = 3$

$^b n = 1$

showed that, in human plasma, CRA13 is mainly (80%) and specifically bound to lipoproteins, especially very low-density lipoprotein (Novartis data on file). Based on the physicochemical properties of CRA13 and its protein-binding characteristics, it is likely that lymphatic transport plays a role in the bioavailability of CRA13, particularly postprandially. Studies to specifically address the issue of lymphatic transport are ongoing.

One of the major factors promoting partitioning of the drug into the lymph is the coadministration of a suitable lipid source to support maximum lipoprotein synthesis in the enterocytes. Therefore, food intake would have the potential to both enhance the overall extent of CRA13 absorption through improved solubilization and to increase the proportion of CRA13 absorbed and transported to the systemic circulation via the intestinal lymph.

Another potential mechanism by which food may enhance drug absorption includes effects on the drug metabolism (Ingwersen et al., 1993). Although the underlying mechanisms are not entirely understood, food may influence drug bioavailability by changing splanchnic blood flow and/or first pass metabolism in the liver (Gershkovich and Hoffman, 2007). In vivo animal studies have demonstrated that CRA13 is subject to extensive hepatic first pass metabolism in dog. Because intestinal lymph drains directly into the venous blood circulation, an enhanced lymphatic transport of such a drug may also improve its bioavailability by bypassing the first pass metabolism.

A longer apparent elimination half-life was observed under fed conditions compared with the fasted administration (Table 3). Considering the high variability in $t_{1/2}$ in the fasted period of the food effect cohort (%CV Geo mean = 94%), any conclusion on apparent terminal elimination half-life should be drawn with extreme caution. However, CRA13 was well tolerated, and the study was stopped at 80 mg on the recommendation of the investigator. There was a dose-dependent increase in the incidence of AEs concomitant with increases in $C_{\text{max}}$, $AUC_{0\text{-}t_{\text{lag}}}$, and $AUC_{0\text{-}\infty}$. The highest incidence was seen with a dose of 80 mg fasted, followed by a dose of 40 mg coadministered with food.

The AE profiles are similar to those known for $\Delta^2$-tetrahydrocan-
CRA13 metabolism in vitro and CRA13 absorption, disposition, and metabolism were assessed by Dr. Gerard Bruin and coworkers who investigated these aspects. Bertrand Rochat provided assistance in the bioanalysis of plasma samples.

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