# A Phase I, Double Blind, Three-Way Crossover Study to Assess the Pharmacokinetic Profile of Cannabis Based Medicine Extract (CBME) Administered Sublingually in Variant Cannabinoid Ratios in Normal Healthy Male Volunteers (GWPK0215)

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**SUMMARY.** Primary objectives of this study were to assess the pharmacokinetic characteristics of CBME when administered sublingually in different ratios, to determine if the pharmacokinetic profiles of THC and its metabolite 11-hydroxy-THC are different when administered sublingually in different formulations, and to characterise the pharmacokinetic profile of CBD when administered with THC in equal amounts.

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[Haworth co-indexing entry note]: "A Phase I, Double Blind, Three-Way Crossover Study to Assess the Pharmacokinetic Profile of Cannabis Based Medicine Extract (CBME) Administered Sublingually in Variant Cannabinoid Ratios in Normal Healthy Male Volunteers (GWPK0215)." Guy, G. W., and P. J. Robson. Co-published simultaneously in *Journal of Cannabis Therapeutics* (The Haworth Integrative Healing Press, an imprint of The Haworth Press, Inc.) Vol. 3, No. 4, 2003, pp. 121-152; and: *Cannabis: From Pariah to Prescription* (ed: Ethan Russo) The Haworth Integrative Healing Press, an imprint of The Haworth Press, Inc., 2003, pp. 121-152. Single or multiple copies of this article are available for a fee from The Haworth Document Delivery Service [1-800-HAWORTH, 9:00 a.m. - 5:00 p.m. (EST). E-mail address: docdelivery@haworthpress.com].

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10.1300/J175v03n04_02

Secondary objectives were to determine if there was a correlation between intoxication levels and plasma concentrations of THC and/or its metabolite 11-hydroxy-THC, and to assess safety and tolerability of CBME when administered sublingually.

Methodology employed a double-blind, randomised, three-way crossover study of placebo, High THC and CBD:THC administered sublingually as a liquid spray. Twenty-four subjects were planned, dosed, completed the study and were analysed.

Test products were $\Delta^9$-tetrahydrocannabinol (THC, formulated as 25 mg THC per ml) with or without cannabidiol (CBD) (formulated as 25 mg CBD + 25 mg THC per ml) formulated in ethanol (Eth):propylene glycol (PG) with peppermint (ppmt) flavouring or matching placebo, administered with a 100 µl pump. Each subject received one single dose of 10 mg THC and one single dose of 10 mg CBD + 10 mg THC plus a single dose of placebo in a randomised manner on three separate occasions. The washout period was six days between each dose. Placebo was Eth:PG in a 50:50 ratio with ppmt flavouring, administered with a 100 µl actuator pump.

Mean plasma concentrations show that following administration of both High THC and CBD:THC formulations CBD and or THC was detectable in plasma in measurable concentrations 15-30 minutes after dosing, although individual subjects showed quite wide variability, 15 to 135 minutes, to appearance measurable concentrations. At all time points up to 180 minutes after dosing mean concentrations of THC were greater following the High THC formulation than CBD:THC. Concentrations of THC were also greater than corresponding concentrations of CBD following the CBD:THC treatment.

There were no statistically significant differences in mean $C_{max}$, $t_{1/2}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ of both THC and 11-hydroxy-THC between the High THC and CBD:THC formulations. THC $T_{max}$ was statistically significantly later following CBD:THC than High THC ($p = 0.014$) and this was the only statistically significant difference in pharmacokinetic parameters between the treatments. The AUC values ($AUC_{0-t}$ and $AUC_{0-\infty}$) for THC show an approximate 8 to 10-fold difference between the lowest and highest subject values while the difference for CBD was approximately 3.5 to 4-fold. Differences in $C_{max}$ were 20 to 30 fold for THC and approximately 14-fold for CBD. Intra-subject differences in values for THC between treatments were smaller though differences in $C_{max}$ of up to 5-fold and 3-fold in AUC ($AUC_{0-t}$ and $AUC_{0-\infty}$) were observed. Other than a single isolated significant difference in $T_{max}$ there were no significant differences in pharmacokinetic parameters between the CBD:THC and High THC formulations. The bioavailability of THC appears to be greater than that of CBD.

Mean intoxication scores on both CBME treatments were very low

throughout the observation period. The majority of subjects scored zero for the majority of assessment points and there were few scores greater than three on the Box Scale 11 (BS-11). Recorded intoxication scores do not seem to show a direct relationship to plasma concentrations of THC and/or 11-hydroxy-THC either within or between subjects. The time of intoxication scores in individual subjects do not seem to relate consistently with the timing of increases in plasma concentrations or maximal concentrations of THC or 11-hydroxy-THC. Neither is there an apparent relationship between subjects reporting intoxication and those with the highest plasma levels of THC or 11-hydroxy-THC.

No subjects withdrew from the study as a result of adverse events and both active and the placebo test treatments were well tolerated. The treatment with the least number of treatment related adverse events was placebo. High THC and CBD:THC had a greater number of subjects who experienced intoxication type adverse events and application site type reactions. The most common overall adverse event experienced was throat irritation, followed by dizziness, somnolence, oral paraesthesia and then headache. All the events were mild and only two events needed any treatment. There were no clinically significant changes from baseline for haematology, biochemistry, vital signs or ECGs.

There was wide inter- and intra-subject variability in pharmacokinetic parameters with up to 10-fold differences in THC AUC between subjects and even greater differences in $C_{max}$. Results suggest that there are no overall statistically significant differences between the pharmacokinetic parameters of High THC and CBD:THC other than a delay in $T_{max}$. Considering the wide inter- and intra-subject variability in pharmacokinetic parameters including $T_{max}$ this is unlikely to be clinically important in a medication that is self titrated by the patient. 

**KEYWORDS.** Cannabinoids, cannabis, THC, cannabidiol, medical marijuana, pharmacokinetics, pharmacodynamics, multiple sclerosis, botanical extracts, alternative delivery systems, harm reduction

## *INTRODUCTION*

Cannabis plants (*Cannabis sativa*) contain approximately 60 different cannabinoids (Association 1997) and in the UK, oral tinctures of cannabis were prescribed until cannabis was made a Schedule 1 con-

trolled substance in the Misuse of Drugs Act, 1971. The prevalence of recreational cannabis use increased markedly in the UK after 1960, reaching a peak in the late 1970s. This resulted in a large number of individuals with a range of intractable medical disorders being exposed to the drug, and many of these discovered that cannabis could apparently relieve symptoms not alleviated by standard treatments. This was strikingly the case with certain neurological disorders, particularly multiple sclerosis (MS). The black market cannabis available to those patients is thought to have contained approximately equal amounts of the cannabinoids $\Delta^9$-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Baker, Gough, and Taylor 1983). The importance of CBD lies not only in its own inherent therapeutic profile but also in its ability to modulate some of the undesirable effects of THC through both pharmacokinetic and pharmacodynamic mechanisms (McPartland and Russo 2001). MS patients claimed beneficial effects from cannabis in many core symptoms, including pain, urinary disturbance, tremor, spasm and spasticity (Association 1997). The MS Society estimated in 1998 that up to 4% (3,400) of UK MS sufferers used cannabis medicinally (Lords 1998).

Cannabinoid clinical research has often focussed on synthetic analogues of THC, the principal psychoactive cannabinoid, given orally. This has not taken the possible therapeutic contribution of the other cannabinoid and non-cannabinoid plant components into account, or the slow and unpredictable absorption of cannabinoids via the gastrointestinal tract (Agurell et al. 1986). Under these conditions it has been difficult to titrate cannabinoids accurately to a therapeutic effect. Research involving plant-derived material has often reported only the THC content (Maykut 1985) of the preparations, making valid comparisons between studies difficult. GW Pharma Ltd (GW) has developed cannabis based medicine extracts (CBMEs) derived from plant cultivars that produce high and reproducible yields of specified cannabinoids. CBMEs contain a defined amount of the specified cannabinoid(s), plus the minor cannabinoids and also terpenes and flavonoids. The specified cannabinoids constitute at least 90% of the total cannabinoid content of the extracts. The minor cannabinoids and other constituents add to the overall therapeutic profile of the CBMEs and may play a role in stabilising the extract (Whittle, Guy, and Robson 2001). Early clinical studies indicated that sublingual dosing with CBME was feasible, well tolerated and convenient for titration. The concept of self-titration was readily understood by patients and worked well in practice. Dosing patterns tended to resemble those seen in the patient controlled analgesia

technique used in post-operative pain control; with small doses administered as and when patients require them, up to a maximal rate and daily limit (Pharmaceuticals 2002). The Phase 2 experience has supported some of the wide-range of effects reported anecdotally for cannabis. It has also shown that for most patients the therapeutic benefits of CBMEs could be obtained at doses below those that cause marked intoxication (the 'high'). This is consistent with experience in patients receiving opioids for pain relief, where therapeutic use rarely leads to misuse (Porter and Jick 1980; Portenoy 1990). Onset of intoxication may be an indicator of over-titration. However the range of daily dose required is subject to a high inter-individual variability.

SATIVX (1:1 THC:CMD CBME) was administered as an oromucosal spray, and contains an equal proportion of THC and CBD, similar to the cannabinoid profile of the cannabis thought to be most commonly available on the European black market (Porter and Jick 1980; Portenoy 1990). The High-THC CBME was administered as an oromucosal spray, and contains over 90% of cannabinoids as THC. Placebo was administered as sublingual liquid spray and was used as a reference treatment to reduce bias.

GWPK0215 was a Phase I clinical study that primarily aimed to assess the PK profiles of each test treatment. It was also designed to assess safety and tolerability of the test treatments.

Primary objectives of this study were to assess the PK characteristics of CBME when administered sublingually in different ratios, to determine if the PK profiles of THC and its metabolite, 11-hydroxy-THC, are different when administered sublingually in different formulations, and to characterise the PK profile of CBD when administered with THC in equal amounts. Secondary objectives were to determine if there is a correlation between intoxication levels and plasma concentrations of THC and/or its metabolite 11-hydroxy-THC, and also to assess safety and tolerability of CBME when administered sublingually.

## *OVERALL STUDY DESIGN AND PLAN–DESCRIPTION*

The study was a double-blind, three-period, three-way randomised crossover using single doses of 10 mg THC, 10 mg CBD + 10 mg THC and placebo. The test treatment was administered sublingually as a liquid spray according to the pre-determined randomisation scheme. The washout period between each dose was six days.

High THC CBME was formulated in 50% ethanol (Eth), 50% propylene glycol (PG) at a concentration of 25 mg THC per ml of Eth:PG with peppermint flavouring. It was delivered via pump action spray at 100 µl per actuation

SATIVEX (1:1 THC:CBD CBME) was formulated in 50% ethanol (Eth), 50% propylene glycol (PG) at a concentration of 25 mg CBD + 25 mg THC per ml of Eth:PG with peppermint flavouring. It was delivered via pump action spray at 100 µl per actuation. Placebo was formulated as Eth:PG in a 50:50 ratio with peppermint flavouring delivered via pump action spray at 100 µl per actuation.

Subjects were required to undergo a pre-study screen no more than 21 days prior to first dose administration to determine their eligibility to take part in the study. Only those subjects who were healthy and complied with all the study requirements were deemed eligible for participation.

These test treatments were chosen as they were the formulation and treatments that were used in the GW Pharmaceuticals clinical programme. The dose administered in this study (10 mg CBD and/or 10 mg THC) was chosen as this is a high single dose of the test treatment when used by patients in a self-titrated regime and is known to be well tolerated by normal healthy subjects.

A randomised cross-over design was chosen to enable both inter- and intra-subject comparisons of PK and pharmacodynamic data and to reduce period effect. The study was double-blind to ensure no bias could be introduced when assessing adverse events (AEs) and pharmacodynamic effects.

A six-day washout was chosen to ensure all cannabinoids were below the limit of quantification and eased the scheduling of the study in the clinical unit.

GW specified that only subjects with previous experience with the effects of cannabis be included in this trial to ensure that subjects recognised the adverse effects (in particular the 'recreational high') they may experience as a result of being dosed with the test treatments.

For inclusion in the study subjects were required to fulfil ALL of the following criteria:

i. Adult male aged between 18 and 50 years and BMI of between 19 and 30 kg/$m^2$.
ii. Had given written informed consent.
iii. Had experienced the effects of cannabis more than once.

Subjects were deemed not acceptable for participation in the study if any of the following criteria applied:

i. Had a presence of cardiovascular, haematological, hepatic, gastro-intestinal, renal, pulmonary, neurological or psychiatric disease.
ii. Had a history or presence of schizophrenic-type illness.
iii. Had a history or presence of drug or alcohol abuse in the past 12 months.
iv. Had been hospitalised in the three months prior to dosing.
v. Had lost or donated > 400 ml of blood in the three months prior to dosing.
vi. Had participated in a clinical trial in the three months prior to dosing.
vii. Had a history or presence of allergies to cannabis and/or its metabolites.
viii. Were taking or had taken a course of prescribed medication in the four weeks prior to dosing.
ix. Were taking or had taken over-the-counter medication, excluding paracetamol and/or vitamins but including mega dose vitamin therapy, within the week before administration of the first dose.
x. Had blood and/or urinalysis results at screening, which, in the opinion of the Principal Investigator were clinically significant.
xi. Had a resting blood pressure (BP) of > 150/90 mmHg or < 90/50 mmHg and a pulse of > 100 beats per minute (BPM) or < 40 BPM.
xii. Had an ECG which, in the opinion of the Principal Investigator was clinically significant.
xiii. Smoked ≥ 5 cigarettes or used the equivalent in tobacco per day.
xiv. Regularly consumed > 28 units of alcohol per week.

Subjects were required to agree to the following:

i. Using barrier methods of contraception during and for three months after completion of the study.
ii. Abstaining from consuming all foods and beverages containing caffeine and/or alcohol for 36 h before until the end of each confinement period.
iii. Abstaining from taking any medications (prescription and/or over-the-counter) and drugs, for the duration of the study.

iv. Not smoking or using tobacco products during each confinement period.
v. Not donating blood in the three months after completion of the study.
vi. Not participating in another clinical trial for 3 months after completion of this one.

The subjects were free to withdraw from the study without explanation at any time and without prejudice to future medical care. Subjects may have been withdrawn from the study at any time if it was considered to be in the best interest of the subject's safety.

A single dose of 10 mg THC, a single dose of 10 mg CBD + 10 mg THC and a single dose of placebo were administered sublingually to each of 24 subjects on three separate occasions in a randomised manner. Each single dose consisted of a series of four actuations of 100 μl volume each (2.5 mg CBD and/or 2.5 mg THC per actuation) and each actuation was administered five minutes apart. Each subject received all of the test treatments once. Each vial was identified with no less than study number, subject number, period number, batch number and expiry date.

Subjects were randomised to a dose sequence using a Williams Square Design provided by GW. All subjects were randomised to receive a single dose of each of the test treatments once in each of the three periods.

The dosing regime and doses chosen are well tolerated by both subjects and patients. The dose given has been previously used in other GW Phase I studies and has been shown to produce both quantifiable drug concentrations in plasma and pharmacodynamic effects.

The subjects were dosed in three groups of eight subjects (Group 1; Subjects 101-108, Group 2; Subjects 109-116 and Group 3; Subjects 117-124). The test treatments were administered in the morning of each dosing day according to the randomisation scheme. Subjects were dosed in the morning to allow blood samples to be taken and procedures to be carried out up to 24 h post-dose with minimal disruption to the subjects during the night. A minimum of six days washout between each dose was specified as previous data and drug of abuse screens have indicated that concentrations of each cannabinoid from a single dose of CBME are below the limit of quantification by this time.

The study was double-blind. Unblinding envelopes were retained at the study site and a duplicate set was retained at GW. All subjects completed the study without experiencing any serious adverse events (SAEs)

and unblinding was not required. Upon completion of the in-life phase of the study all unblinding envelopes were returned to GW intact.

Only one subject (Subject 101) took medication during the study.

Subjects were dosed by the Principal Investigator or suitably trained designee. Subjects were instructed to allow each spray of the study formulation to absorb under their tongue and not to swallow, if possible, until the drug had been absorbed. The actual time of administration of each actuation was recorded in the CRF (Case Report Form) and the dosing procedure was witnessed by a dose verifier. All subjects received all of the scheduled doses and there were no deviations from the dosing regimen.

Only those subjects who were healthy and complied with all the study requirements were deemed eligible for participation. The screening procedures comprised the following assessments/measurements: The subjects' date of birth, sex, race, height, weight, BMI, previous cannabis experience, tobacco and alcohol habits were recorded. Subjects were asked to provide details of any drugs, vitamins or medications they had taken in the four weeks prior to screening or were taking at the time of screening.

Details of their previous medical history were also recorded. Subjects underwent a physical examination to determine if there were any abnormalities in any body systems. BP (systolic/diastolic) and pulse were measured after the subject had been seated for no less than 2 minutes. Oral temperature was also measured. A 12-lead ECG (electrocardiogram) was taken for each subject. At least the following ECG parameters were recorded: HR (heart rate), PR, $QT_c$ and QRS intervals. The ECGs were expertly read by Cardio Analytics for ventricular rate, PR interval, QRS duration and QT interval.

Subjects were required to provide a urine sample for routine urinalysis to include protein glucose, ketones, bilirubin, nitrites, blood, urobilinogen, haemoglobin (Hb), and Ph. Microscopy was required to be carried out on any abnormal samples. The samples provided were also screened for alcohol and drugs of abuse, including methadone, benzodiazepines, cocaine, amphetamines, THC, opiates and barbiturates

A blood sample was taken in an EDTA blood tube for full haematology analysis. A blood sample was taken in a gel blood tube for clinical chemistry analysis. The following clinical chemistry parameters were measured: sodium, potassium, urea, creatinine, total bilirubin, alkaline phosphatase, total protein, calcium, gamma glutamyl transferase (GGT), albumin, aspartate aminotransferase (AST), alanine aminotransferase

(ALT). A blood sample was taken in a gel blood tube to screen for the serological presence of past or present Hepatitis B and/or C.

Subjects were required to arrive at the clinic approximately 12 hours prior to dosing for each study period. Each subject's health status was updated and pre-dose procedures (health status update, BP and pulse, alcohol and drug of abuse screen, ECG, Box Scale-11 and blood sample for plasma concentration analysis) were carried out. Only subjects who complied with the requirements of the study were accepted for inclusion in the study.

Blood samples (5 ml) for pharmacokinetic analysis were collected into lithium heparin blood tubes via indwelling cannula or individual venipuncture. Samples were placed immediately into an ice bath until centrifuged (3000 RPM for 10 min at 4°C). The resultant plasma was decanted into two identical pre-labelled silanised amber glass plasma tubes and stored in a freezer at −20°C until shipped to the analytical laboratory.

Blood samples were collected pre-dose and at the following times post start of dosing: 15, 30 and 45 m and 1 h, 1 h 10 m, 1 h 20 m, 1 h 30 m, 1 h 40 m, 1 h 50 m, 2 h, 2 h 15 m, 2 h 30 m, 3, 6, 9, 12 and 24 h post first actuation in each period. Plasma concentrations of CBD, THC and 11-hydroxy-THC were measured in each plasma sample.

## *SAFETY ASSESSMENTS*

Each subject was required to provide a urine sample for a urine drug screen at check in for each dosing period. The drug screen was required to be negative for all drugs pre-dose Period 1. For Periods 2 and 3, positive THC results may have occurred due to administration of test treatment in the previous period and therefore screening for THC was not carried out post Period 1. The urine sample was required to be negative for all other drugs for the subject to be eligible to continue.

The urine sample provided at check-in for each study period for the drug screen was also screened for alcohol. All subjects were required to have a negative alcohol screen to be considered eligible to continue in the study.

12-Lead ECGs were taken for each subject at the following times: pre-dose, 1, 2, 12 and 24 h post-dose. The $QT_c$ intervals for all ECGs were read manually by Cardio Analytics, ITTC Building 2, Tamar Science Park, 1 Davy Road, Derriford, Plymouth, PL6 8BX. Subjects'

blood pressure and pulse were measured pre-dose and at 15, 30 and 45 min, 1, 1.5, 2, 3, 6, 9, 12 and 24 h post start of dosing.

### *Adverse Effects*

Subject health was monitored continuously throughout the study for AEs and pharmacodynamic effects and subjects were encouraged to inform the clinical staff of any changes in their health as soon as possible. In addition, subjects' health was monitored by asking non-leading questions pre-dose and at the following times post-dose: 15, 30 and 45 min, 1, 1.5, 2, 2.5, 3, 6, 9, 12 and 24 h post-dose. Any concomitant medications taken during the study were recorded in the subjects CRF.

### *Box Scale-11 for Intoxication*

Subjects were required to complete a Box Scale 11 (BS-11) to describe how intoxicated they were feeling at the following times: pre-dose, 15 m, 30 m, 45 m, 1 h, 1 h 30 m, 2 h, 3 h, 6 h, 9 h, 12 h and 24 h post start of dosing.

### *Palatability/Dose Questionnaire*

As soon as possible after dosing, subjects were asked to complete a questionnaire about the palatability and sensation of the test treatment experienced during and immediately after dosing.

### *Food and Beverages*

A standard low fat breakfast approximately 30 min before dosing for each subject. From 15 min prior to 15 min post-dosing, subjects were required to abstain from consuming food and beverages. Thereafter, decaffeinated beverages and snacks, e.g., digestive biscuits, were available *ad libitum* throughout each confinement period. Subjects were provided with standard meals at approximately 4 and 10 h post-dose (lunch and dinner, respectively) (Table 1).

### *Check-Out Procedures*

After completion of the 24 h study procedures at the end of Periods 1 and 2 and if deemed by the Investigator to be well enough to leave, subjects were discharged from the clinical unit. Prior to discharge, any on-

TABLE 1. Menu

| *Day 1** | | | *Day 2* |
|---|---|---|---|
| *Breakfast* | *Lunch* | *Dinner* | *Breakfast* |
| Orange juice | Jacket potato | Chicken | Orange juice |
| | Cheese | Quorn Fillet (v) | |
| Cereals | Coleslaw and Salad | Roast Potatoes | Cereals |
| toast with butter & preserves | | peas and carrots | toast with butter & preserves |
| | Yoghurt | gravy | |
| | | gravy (v) | |
| tea/coffee** | tea/coffee** | | tea/coffee** |
| orange/lemon | orange/lemon | Peach melba ice cream sundae | orange/lemon |
| | | tea/coffee** | |
| | | orange/lemon | |

NB: At each admission (Day -1) subjects were permitted 2 digestive biscuits, decaffeinated tea/coffee and orange/lemon
*Digestive Biscuits and Drinks available throughout the day ** decaffeinated v = vegetarian

going AEs were updated and follow up arranged if required. Prior to Period 3 discharge, subjects were required to undergo a physical examination, blood samples were taken for haematology and clinical chemistry, urinalysis was carried out, a 12-lead ECG was taken and vital signs recorded as per screening. Ongoing AEs were updated and if required arrangements were made to follow up with the subjects after they left the clinical unit.

## *DATA QUALITY ASSURANCE*

### *Study Monitoring*

All details regarding the study were documented within individual CRFs provided by GW for each subject. All data recorded during the study were checked against source data and for compliance with Good Clinical Practice (GCP), internal Standard Operating Procedures (SOPs), working practices and protocol requirements. Monitoring of the study progress and conduct was ongoing throughout the study. Monitoring was conducted by the Clinical Department of GW and was conducted

according to GW SOPs. An initiation visit was carried out prior to the start of the study to train site clinical staff on CRF completion, dosing and AE procedures. Training was provided by GW throughout the study as required. Haematology and clinical chemistry analysis were carried out by Leicester General Hospital

### *Investigator Responsibilities*

The Investigator was responsible for monitoring the study conduct to ensure that the rights of the subject were protected, the reported study data were accurate, complete and verifiable and that the conduct of the study was in compliance with ICH GCP. At the end of the study the Principal Investigator reviewed and signed each CRF declaring the data to be true and accurate. If corrections were made after review the Investigator acknowledged the changes by re-signing and dating the CRF.

### *Clinical Data Management*

All study data were collected by GW, who were responsible for evaluation, collation and analysis. Data were subject to quality control procedures. All data were double entered into a Microsoft® Excel 2000 spreadsheet with 10% quality control checks according to GW SOPs. Clinical Quality Audits were carried out by the GW Quality Assurance Department, two Quality Assurance evaluation were carried out and the Pharmacovigilance function was the subject of an internal process audit.

### *Pharmacokinetic Analysis*

All subjects who were dosed and had no more than two missed blood samples were deemed evaluable for, and were included in, PK analyses. All analyses and summary statistics were carried out and derived using SAS v8. All p-values quoted are two-sided. Summary statistics were calculated for each mean PK parameter and treatment (arithmetic mean, N, SD, CV%, minimum, maximum for all parameters and additionally the geometric mean for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and $C_{max}$). $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and $C_{max}$ were natural log transformed prior to analysis, $T_{max}$ and $t_{1/2}$ were analysed untransformed. For the analytes THC and 11-hydroxy-THC, each parameter was analysed using analysis of variance (ANOVA) with subject and treatment as factors (for High THC and CBD:THC). Least square means are presented for each test treatment. Point estimates of the differences between least square means are presented with

the corresponding 95% confidence intervals. For log transformed variables, the contrasts were also back transformed to provide ratios and corresponding 95% confidence intervals. For the analyte CBD which was measurable for only the CBD:THC test treatment, the data are presented descriptively only. $K_{el}$ is presented descriptively only.

### *Pharmacodynamic Analysis*

All subjects who completed at least one study period were evaluable for pharmacodynamic analysis. Intoxication, measured by Box Scale-11, was summarised by treatment group. Means and standard deviations were also calculated.

## *SAFETY ANALYSIS*

### *Adverse Events*

AEs were coded by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. These are summarised by test treatment for treatment emergent all causality and treatment emergent treatment related AEs showing the number of subjects with at least one AE and the number of subjects with at least one AE by preferred term within system organ class.

### *Clinical Laboratory Tests*

Laboratory data collected pre- and post-study are summarised descriptively at each of the two time-points and also as the change post-study compared to pre-study.

### *Concomitant Medications*

Subject 101 took concomitant medications between Periods 2 and 3.

### *Blood Pressure, Pulse and Oral Temperature*

Vital signs (pulse, systolic BP, diastolic BP and oral temperature) were monitored. BP and pulse are presented descriptively at each time point up to 12 h post-dose for each test treatment.

### *12-Lead ECG*

ECG parameters (HR, PR interval, QT interval, $QT_c$ and QRS width) were monitored descriptively (N, mean, SD, median, minimum, maximum) pre-study and at each time point up to 12 h post-dose for each test treatment. In addition, $QT_c$ values were classified as either normal, borderline or prolonged. For $QT_c$, absolute values and changes from pre-dose were categorised as borderline, normal, prolonged according to Committee for Proprietary Medicinal Products (CPMP) guidelines.

### *Palatability Questionnaire*

Each question of the palatability questionnaire was been presented descriptively using frequency tables for each test treatment.

### *Determination of Sample Size*

No formal sample size calculation was carried out for this study. The number of subjects is considered to be sufficient to provide information on the pharmacokinetics of the two formulations.

### *Changes in the Conduct of the Study or Planned Analyses*

A Statistical Analysis Plan (SAP) was not produced prior to statistical analysis as detailed in the protocol and the statistical analyses were carried out as indicated in the protocol with the exception of the following:

1. The mean profile with time curve for vital signs for each treatment is not presented.
2. The data was not summarised using the AUEC for blood pressure and pulse rate calculate using the trapezoidal rule.
3. The AUEC was not analysed using the analysis of variance with factors for subject, period and treatment

## *STUDY SUBJECTS*

### *Disposition of Subjects*

Twenty-four healthy male subjects were required to complete the study in its entirety. Twenty-four subjects were randomised and all of

those subjects completed the study. No subjects withdrew from the study and no replacements were required.

### *Protocol Deviations*

Three significant deviations occurred during the study as follows.

1. Post-study oral temperature was not recorded in accordance with ICH GCP, therefore the reliability of the data was not known and was not reported. All subjects were assessed by a physician prior to discharge and all were deemed to be well.
2. On May 18, 2002 (Group 2, Period 2) some blood samples for plasma concentration analysis were taken in sodium heparin blood tubes in error. The analytical laboratory carried out validation testing for use of the sodium heparin tubes and confirmed that changing the blood collection tubes from lithium heparin to sodium heparin did not alter the extraction efficiency or change in analytical methodology required.
3. Subject 101 took two single oral doses (400 mg each) of ibuprofen tablets on two consecutive days (May 18 and 19, 2002) for coryza. This was during the restriction period between Periods 2 and 3. Investigator's judgement was made and the subject was deemed eligible to continue in the study.

These protocol deviations were not considered to affect the integrity of the study.

### *Plasma Concentration, Pharmacokinetic, and Pharmacodynamic Evaluation*

All twenty-four subjects (101 to 124) who were randomised completed the study. Subjects were considered evaluable if no more than one blood sample per period was missed. No blood samples were missed therefore all subjects were included in the data analysis.

All subjects included in the study complied with all demographic and baseline requirements. Each test treatment was administered by suitably trained study site clinical staff. No deviations to the dosing regimen were noted for any subject throughout the study.

## INDIVIDUAL PLASMA CONCENTRATION DATA, PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

### Analysis of Plasma Concentration Results

Plasma samples were analysed for CBD, THC and 11-hydroxy-THC according to the analytical protocol (Figure 1). Plasma concentration results are shown in tabular form (Table 2) and concentration-time graphs produced from these data (Figures 2-6).

The Lower Limit of Quantification (LLOQ) for this study was 0.1 ng/ml. The actual values measured were used when creating graphs.

Mean plasma concentrations of the relevant cannabinoids for the formulations are summarised in Table 2.

Mean plasma concentrations show that following administration of both High THC and CBD:THC formulations (Figure 2, Figure 3), THC was detectable in plasma in measurable concentrations 30-45 min after dosing, although subjects showed quite wide variability with both formulations (15-70 min). At all time points up to 180 min after dosing, mean concentrations of THC were greater following the High THC formulation (Figure 2) than CBD:THC (Figure 3). Mean 11-hydroxy-THC plasma levels (Figure 4, Figure 5) seemed generally to reflect levels of THC and were similarly greater following High THC (Figure 4) at most time points up to 180 min.

Mean plasma levels of CBD were above the level of detection about 45 min after dosing and were approximately 30-50% lower than the cor-

FIGURE 1

The following PK parameters were calculated for CBD, THC and 11-hydroxy-THC:

| | |
|---|---|
| $T_{max}$ | Time to the maximum measured plasma concentration. |
| $C_{max}$ | Maximum measured plasma concentration over the time span specified. |
| $t_{1/2}$ | Putative effective elimination half life (the initial descending portion of each plasma concentration-time graph). |
| $AUC_{0-t}$ | The area under the plasma concentration versus time curve, from time zero to 't' (where t = the final time of positive detection, $t \leq 24$ h) as calculated by the linear trapezoidal method. |
| $AUC_{0-\infty}$ | The area under the plasma concentration versus time curve from zero to t calculated as $AUC_{0-t}$ plus the extrapolated amount from time t to infinity. |
| $K_{el}$ | Elimination rate. |

TABLE 2. Mean Plasma Concentration Data

| Time (min) | Analyte | | | | |
|---|---|---|---|---|---|
| | CBD | THC | | 11-Hydroxy-THC | |
| | Test Treatment | | | | |
| | CBD:THC | High THC | CBD:THC | High THC | CBD:THC |
| 0 | 0.00 | 0.01 | 0.00 | 0.00 | 0.00 |
| 15 | 0.00 | 0.02 | 0.01 | 0.01 | 0.00 |
| 30 | 0.05 | 0.13 | 0.06 | 0.22 | 0.10 |
| 45 | 0.21 | 0.47 | 0.30 | 0.81 | 0.53 |
| 60 | 0.38 | 0.77 | 0.61 | 1.19 | 1.01 |
| 70 | 0.39 | 1.11 | 0.61 | 1.34 | 1.06 |
| 80 | 0.52 | 1.26 | 0.75 | 1.57 | 1.23 |
| 90 | 0.62 | 1.65 | 0.89 | 1.86 | 1.44 |
| 100 | 0.84 | 2.15 | 1.21 | 2.33 | 1.59 |
| 110 | 1.21 | 2.60 | 1.78 | 2.53 | 1.73 |
| 120 | 1.15 | 2.82 | 1.69 | 2.65 | 1.90 |
| 135 | 1.27 | 2.87 | 1.80 | 2.45 | 2.14 |
| 150 | 1.37 | 2.93 | 1.93 | 2.77 | 2.52 |
| 180 | 2.04 | 4.02 | 2.72 | 3.51 | 2.93 |
| 360 | 1.34 | 1.17 | 1.82 | 1.74 | 2.38 |
| 540 | 0.49 | 0.32 | 0.51 | 0.67 | 1.02 |
| 720 | 0.24 | 0.19 | 0.21 | 0.44 | 0.58 |
| 1440 | 0.00 | 0.03 | 0.01 | 0.16 | 0.16 |

responding levels of THC (Figure 6). Again there was quite wide variability between subjects with the time of first measurable concentration ranging from 30 to 135 min.

Following administration of High THC CBME, no subject had measurable concentrations of CBD at any time point. Following placebo, a single blood sample (60 min) from Subject 115 recorded levels of THC, CBD and 11-hydroxy-THC. Also, on the placebo dosing day, Subject 121 had measurable concentrations of THC pre-dose and at all time points post-dose. 11-Hydroxy-THC was also detected pre-dose and all time point up to 3 h post-dose. Subject 115 also had one value for THC (0.19 ng/ml at 60 min) and 11-hydroxy-THC (0.23 ng/ml at 60 min) fol-

FIGURE 2. GWPK0215 Mean Plasma THC Concentrations Following Administration of High THC

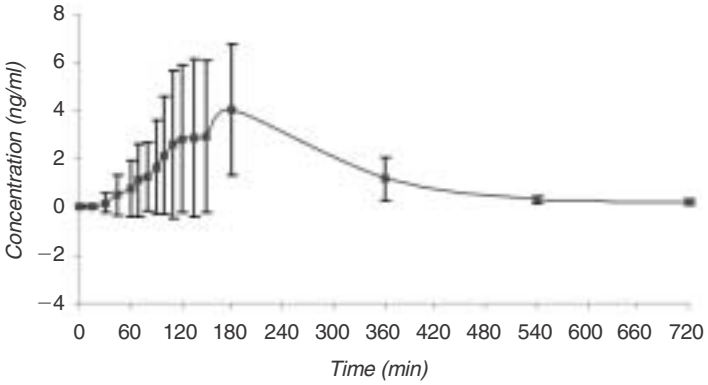
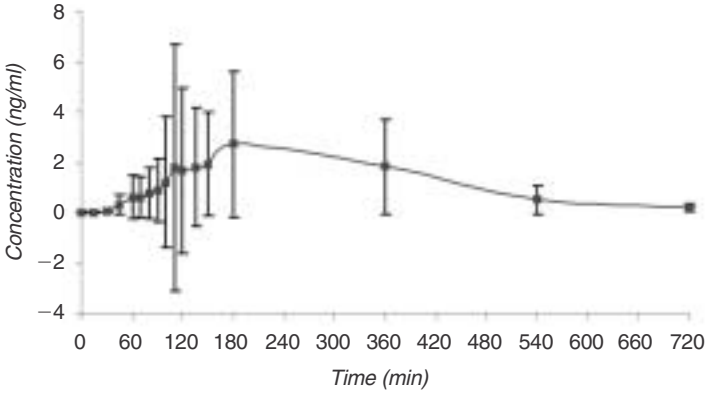



FIGURE 3. GWPK0215 Mean Plasma THC Concentrations Following Administration of CBD:THC




lowing administration of the placebo treatment which was above the LLOQ. The placebo treatment for subjects 115 and 121 was Period 3 and therefore followed previous High THC and CBD:THC dosing.

### *Analysis of Pharmacokinetic Parameters*

PK parameters were calculated using WinNonlin® Professional 3.1. The model used was a non-compartmental, linear trapezoidal analysis.

FIGURE 4. GWPK0215 Mean Plasma 11-Hydroxy-THC Concentrations Following Administration of High THC

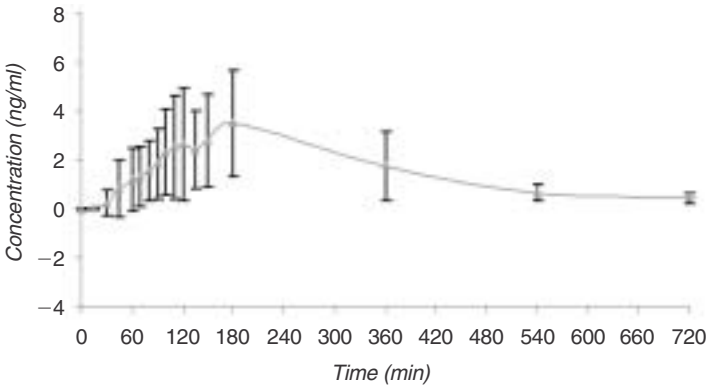
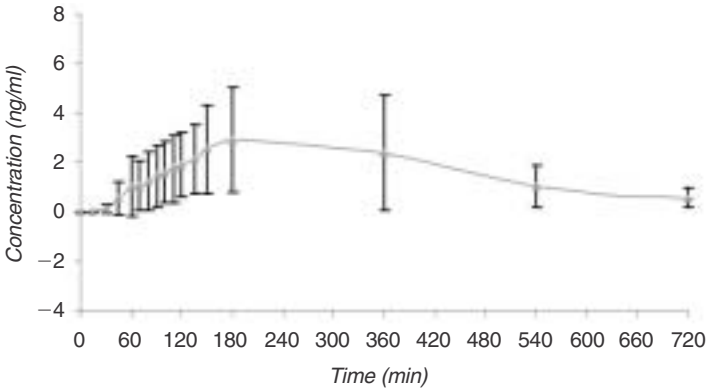



FIGURE 5. GWPK0215 Mean Plasma 11-Hydroxy-THC Concentrations Following Administration of CBD:THC




Values below the LLOQ are not considered reliable and therefore were not used when calculating PK parameters. Mean values are presented in Table 3.

Following dosing with the CBD:THC test treatment the mean $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ of CBD were lower than the corresponding mean results for THC though $T_{max}$ was similar. The $t_{1/2}$ of CBD (108.72 min) was longer than the $t_{1/2}$ of THC (84.23 min).

The PK values for each individual showed considerable inter- and

FIGURE 6. GWPK0215 Mean Plasma CBD Concentrations Following Administration of CBD:THC

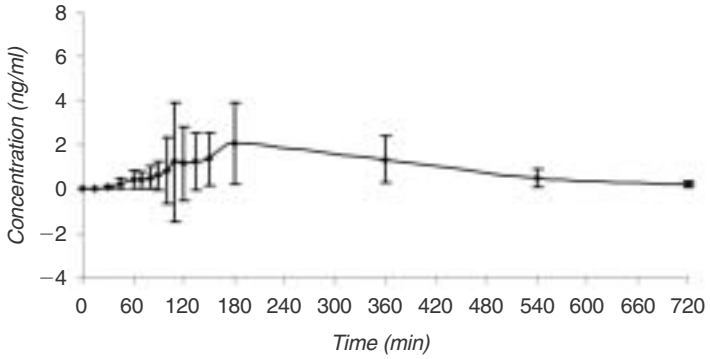



TABLE 3. Mean Pharmacokinetic Parameters

| *Treatment* | *$T_{max}$ (min)* | *$C_{max}$ (ng/ml)* | *$t_{1/2}$ (min)* | *$AUC_{0-t}$ (min*ng/ml)* | *$AUC_{0-\infty}$ (min*ng/ml)* |
|---|---|---|---|---|---|
| | *Mean Pharmacokinetic Parameters for CBD* | | | | |
| CBD:THC | 253 | 3.33 | 108.72 | 680.61 | 718.46 |
| | *Mean Pharmacokinetic Parameters for THC* | | | | |
| High THC | 188 | 5.66 | 73.09 | 987.47 | 1005.90 |
| CBD:THC | 263 | 4.90 | 84.23 | 894.80 | 918.81 |
| | *Mean Pharmacokinetic Parameters for 11-Hydroxy-THC* | | | | |
| High THC | 179 | 4.81 | 109.38 | 1300.47 | 1334.41 |
| CBD:THC | 230 | 4.49 | 130.11 | 1423.20 | 1463.67 |

Mean $C_{max}$, $t_{1/2}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ of both THC and 11-hydroxy-THC were not statistically significantly different following the High THC and CBD:THC formulations. $T_{max}$ of both THC and 11-hydroxy-THC was later following the CBD:THC than High THC formulation though only the difference in THC $T_{max}$ reached statistical significance ($p = 0.014$).

intra-subject variation in all parameters. The variability appeared to be greater for THC than for CBD. The AUC values ($AUC_{0-t}$ and $AUC_{0-\infty}$) for THC show an approximate 8 to 10-fold difference between the lowest and highest subject values while the difference for CBD was approximately 3.5 to four-fold. Differences in $C_{max}$ were 20 to 30-fold for THC and approximately 14-fold for CBD. Intra-subject differences in individual values for THC between treatments were smaller though differ-

ences in $C_{max}$ of up to 5-fold and 3-fold in AUC ($AUC_{0-t}$ and $AUC_{0-\infty}$) were observed.

### *Analysis of Intoxication Results*

For each test treatment period, intoxication was measured using BS-11 with a score of zero indicating no intoxication and a score of 10 indicating maximum intoxication. Mean intoxication results are presented in Table 4.

On the placebo day Subject 114 scored pre-dose intoxication at a level of 5 and from 45-90 min scored a level of 6 then 5 for the remainder of the 24 h period. Two other subjects (108 and 124) scored an increased level intoxication of 1 at some time points (45-60 min and 15-60 min, respectively). Mean levels of intoxication remained low for both active test treatments throughout each 24 h post-dose period.

Following administration of High THC CBME, individual intoxication scores were below five. Seven subjects scored no intoxication at all assessment points (no score > zero). Seven subjects had at least one

TABLE 4. Mean Intoxication Following Administration of Each Test Treatment

| *Time (min)* | *Mean Intoxication* | | |
|---|---|---|---|
| | *Placebo* | *High THC* | *CBD:THC* |
| 0 | 0.2 | 0.0 | 0.0 |
| 15 | 0.3 | 0.3 | 0.2 |
| 30 | 0.3 | 0.4 | 0.2 |
| 45 | 0.3 | 0.5 | 0.3 |
| 60 | 0.3 | 0.5 | 0.5 |
| 90 | 0.3 | 0.5 | 0.6 |
| 120 | 0.2 | 0.6 | 0.8 |
| 180 | 0.2 | 0.9 | 0.8 |
| 360 | 0.2 | 0.7 | 1.2 |
| 540 | 0.2 | 0.2 | 0.4 |
| 720 | 0.2 | 0.0 | 0.1 |
| 1440 | 0.2 | 0.0 | 0.0 |

Mean levels of intoxication remained below 1 throughout the 24h period following placebo dosing. Mean intoxication scores on both test treatments were very low throughout the observation period with increased levels (mean score of 1) only between 60 and 360 minutes after dosing.

score of three or greater though in four subjects this was at a single assessment point. One subject (Subject 115) recorded a score of three or greater at two consecutive time points, Subject 101 recorded scores of three between 45 and 180 min post-dose and Subject 121 recorded scores of three or greater between 30 and 180 min post-dose. The highest individual intoxication score was five (Subject 121 at 45 and 60 minutes post-dose).

Following administration of CBD:THC, nine subjects scored no intoxication at all assessment points. Ten subjects had at least one score of three or greater though in five this was at a single assessment point. Five subjects (subjects 101, 111, 112, 113 and 116) recorded a score of three or greater at two consecutive time points. The highest individual intoxication score was 10 (Subject 112 at a single time point post-dose).

Recorded intoxication scores do not seem to show a direct relationship to plasma concentrations of THC and/or 11-hydroxy-THC either within or between subjects. The times of intoxication scores in individual subjects do not seem to relate consistently with the timing of increases in plasma concentrations or maximal concentrations of THC or 11-hydroxy-THC. Neither is there an apparent relationship between subjects reporting intoxication and those with the highest plasma levels of THC or 11-hydroxy-THC. The maximum intoxication score of 10 reported by Subject 112 occurred 360 minutes post-administration of CBD:THC. This maximal intoxication score was not associated with any report of AEs typical of intoxication (e.g., somnolence, dizziness). Vital signs at this time were only a little changed from pre-dose–pulse 68 (−4), systolic BP 106 (−16) diastolic BP 63 (−4) and do not suggest significant cannabinoid effects. However, the score of 10 coincided with a substantial increase in plasma levels of both THC (3.56 ng/ml) and 11-hydroxy-THC (3.96 ng/ml) compared with both the previous (0.21 and 0.48 ng/ml, respectively) and subsequent measurements (0.77 and 1.88 ng/ml, respectively) at which much lower intoxication scores were reported (0 and 3, respectively). On the day that the High THC was administered the highest intoxication score recorded by this subject was three at 6 h post-dose even though during this dosing period higher plasma levels of THC (2.45 ng/ml) were recorded compared with the CBD:THC test treatment. Plasma levels of 11-hydroxy-THC were a little lower on this occasion.

### *Analysis of Safety Parameters*

For each of the BP and pulse parameters descriptive statistics (n, mean, SD, median, minimum and maximum) were presented at each

time point by test treatment. In addition, the calculations were performed for the absolute change from pre-dose. Mean values and mean changes from baseline were similar across all treatments.

Descriptive statistics (n, mean, SD, median, minimum and maximum) were recorded for the ECG parameters (heart rate, PR interval, QT interval and QRS width) pre-dose and at each time point by test treatment. ECG intervals were expertly read by Cardio Analytics for each of the parameters above. There were no notable changes in the ECG parameters.

Eight subjects (33%) rated the placebo test treatment as very unpleasant or unpleasant compared with 18 subjects (75%) for both the THC and CBD:THC treatments.

One subject (4%) thought the placebo treatment had an unpleasant smell compared with four (17%) subjects who thought the High THC treatment smelt unpleasant. Four (17%) subjects thought the CBD:THC smelt unpleasant and two (8%) very unpleasant. Eleven subjects (46%) for each treatment reported that they were unaware of the smell.

All three test treatments resulted in increased saliva produced with 13 subjects (54%) reporting more saliva following administration of placebo, 16 subjects (66%) with High THC and 17 subjects (71%) with CBD:THC.

The majority of subjects reported that they thought all or most of the test treatments were absorbed in the mouth. Only six subjects (25%) after placebo and High THC thought that some was swallowed and four subjects (17%) after CBD:THC reported some was swallowed.

Most subjects reported no other effects or sensations following administration of each test treatment. Four subjects (17%) reported other effects following administration of placebo, nine subjects (38%) following administration of High THC and 10 subjects (42%) following administration of CBD:THC.

The study was carried out in healthy subjects, none of whom were not taking a regular course of any other medication.

### *Plasma Concentration Conclusions*

Mean plasma concentrations show that following administration of both High THC and CBD:THC formulations, CBD and/or THC were detectable in plasma in measurable concentrations 30-45 min after dosing, although individual subjects showed quite wide variability, 15 to 135 min, to appearance of measurable concentrations. At all time points up to 180 min after dosing mean concentrations of THC were greater

following the High THC formulation than CBD:THC. Concentrations of THC were also greater than corresponding concentrations of CBD following the CBD:THC treatment.

There was considerable individual variability in peak plasma concentrations ($C_{max}$) of both CBMEs. THC $C_{max}$ ranged from 0.69 ng/ml to 14.2 ng/ml and from 0.75 ng/ml to 24.63 ng/ml for the High THC and CBD:THC formulations, respectively. CBD $C_{max}$ following the CBD:THC formulation ranged from 0.96 ng/ml to13.64 ng/ml.

Following administration of High THC CBME, no subject had measurable concentrations of CBD at any time point. Following placebo, a single blood sample (60 min) from Subject 115 had recorded measurable levels of THC, CBD and 11-hydroxy-THC. This sample was re-analysed by the analytical laboratory, however the result may be due to an analytical anomaly. Also on the placebo dosing day Subject 121 had measurable concentrations of THC pre-dose and at all time points post-dose and 11-hydroxy-THC was also measured pre-dose and all time point up to 3 hours post-dose. The placebo treatment in this subject was Period 3 and therefore followed previous High THC and CBD:THC dosing. As there was no carryover from Period 1 to Period 2 in this subject it is unclear whether the THC detected on the placebo day is due to carryover from the previous treatment or a protocol violation in respect of abstention from cannabis.

### *Pharmacokinetic Conclusions*

There were no statistically significant differences in mean $C_{max}$, $t_{1/2}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ of both THC and 11-hydroxy-THC between the High THC and CBD:THC formulations. THC $T_{max}$ was statistically significantly later following CBD:THC than High THC ($p = 0.014$) and this was the only statistically significant difference in PK parameters between the treatments. Following the CBD:THC formulation the $C_{max}$ and AUC of CBD were lower than the corresponding results for THC and the $t_{1/2}$ of CBD (108.72 min) was longer than the $t_{1/2}$ of THC (84.23 min). The PK values for each individual show considerable inter- and intra-subject variation in all parameters. The variability appears to be greater for THC than for CBD. The AUC values ($AUC_{0-t}$ and $AUC_{0-\infty}$) for THC show an approximate 8 to 10-fold difference between the lowest and highest subject values while the difference for CBD was approximately 3.5 to 4-fold. Differences in $C_{max}$ were 20 to 30 fold for THC and approximately 14-fold for CBD. Intra-subject differences in values

for THC between treatments were smaller though differences in $C_{max}$ of up to 5-fold and 3-fold in AUC ($AUC_{0-t}$ and $AUC_{0-\infty}$) were observed.

Other than a single isolated significant difference in $T_{max}$ there were no significant differences in PK parameters between the CBD:THC and High THC formulations. It is unclear whether this significant difference reflects a true or spurious difference in the rates of absorption from the formulations, however, the difference is small and unlikely to be of clinical significance considering the high level of inter- and intra-subject variability in PK. The bioavailability of THC appears to be greater than that of CBD.

### *Intoxication Conclusions*

Mean intoxication scores on both CBME treatments were very low throughout the observation period. The majority of subjects scored zero for the majority of assessment points and there were few scores greater than three on the 11 box scale. One subject recorded a maximal score of 10 at a single (6 h) assessment point following CBD:THC. No AEs were reported and vital signs showed only a slight change from pre-dose at this time, therefore it is uncertain that this reflects an accurate assessment. Recorded intoxication scores do not seem to show a direct relationship to plasma concentrations of THC and/or 11-hydroxy-THC either within or between subjects. The time of intoxication scores in individual subjects do not seem to relate consistently with the timing of increases in plasma concentrations or maximal concentrations of THC or 11-hydroxy-THC. Neither is there an apparent relationship between subjects reporting intoxication and those with the highest plasma levels of THC or 11-hydroxy-THC.

### *Palatability Conclusions*

Both active test treatments, but not placebo, were considered by the majority of the subjects to have an unpleasant or very unpleasant taste. Therefore it can be concluded that the THC and/or CBD, and not the excipients, result in an increased incidence of unpleasant taste. The majority of subjects reported that they were not aware of a smell from the test treatment or that they thought it smelt neither pleasant or unpleasant. Therefore it can be concluded that for the majority of subjects THC and/or CBD in the test treatments used in this study do not have an unpleasant smell. All three test treatments were reported to have increased sa-

liva with a marginally higher incidence from the CBME containing treatments. Most subjects perceived that all or most of the test treatments were absorbed in the mouth.

### *Other Effects or Sensations*

The incidence of other effects or sensations following administration of each test treatment was greater for the CBME treatments than for placebo though the majority of subjects on all treatments reported no such effects.

## *ADVERSE EVENTS (AES)*

### *Brief Summary of Adverse Events*

During the study 87 AEs were recorded in 20 subjects (Table 5) , and of these, 78 were considered to be related to the test treatment (Table 6). Following the administration of placebo, 5 subjects experienced treatment emergent treatment related AEs (Table 6). Following administration of the THC test treatment 16 subjects (66%) experienced treatment emergent treatment related AEs and 18 subjects (75%) experienced treatment emergent treatment related AEs following administration of CBD:THC (Table 6). All the AEs experienced were classified as mild and only one event (Subject 101, coryza) required treatment with medication. None of the subjects withdrew due to AEs. One AE in Subject 107 (left shoulder muscular strain) was lost to follow up.

The most common treatment emergent treatment related AE experienced was throat irritation (six subjects following administration of High THC and eight subjects following administration of CBD:THC), which was not experienced in the subjects during placebo treatment. Dizziness was the second most commonly experienced treatment emergent treatment related AE following the administration of High THC (six subjects). This was followed by somnolence, oral paraesthesia and headache.

### *Analysis of Adverse Events*

Table 7 summarises the number of subjects who reported treatment emergent treatment related AEs by System Organ Class (SOC). There

TABLE 5. Summary of Adverse Events–Treatment Emergent All Causality

| *Event* | *Placebo* | *High THC* | *CBD:THC* |
|---|---|---|---|
| *No. of subjects with ≥ 1 event* | 6 (25.0%) | 16 (66.7%) | 18 (75.0%) |
| *Eye disorders* | 0 | 1 | 0 |
| Vision blurred | | 1 | |
| *Gastrointestinal disorders* | 1 | 9 | 14 |
| Diarrhoea NOS | | | 1 |
| Glossitis | 1 | | 1 |
| Nausea | | 2 | 2 |
| Oral discomfort | | 1 | 1 |
| Oral pain | | 1 | 1 |
| Throat irritation | | 6 | 8 |
| Tongue oedema | | | 1 |
| Vomiting NOS | | | 1 |
| *General disorders and administration site conditions* | 2 | 2 | 1 |
| Feeling of relaxation | 2 | 1 | |
| Lethargy | 2 | 1 | 1 |
| *Injury, poisoning and procedural complications* | 1 | 1 | 2 |
| Drug toxicity NOS | | 1 | 2 |
| Splinter | 1 | | |
| *Musculoskeletal and connective tissue disorders* | 0 | 1 | 2 |
| Muscle strain | | | 1 |
| Muscle twitching | | | 1 |
| Rib fracture | | 1 | |
| *Nervous system disorders* | 4 | 11 | 10 |
| Burning sensation NOS | | 1 | 1 |
| Dizziness | 1 | 6 | 2 |
| Dysgeusia | | | 2 |
| Headache NOS | 2 | | 3 |
| Paraesthesia | | 1 | |
| Paraesthesia oral NOS | 1 | 2 | 3 |
| Somnolence | | 4 | 3 |
| Vasovagal attack (LLT  Syncope vasovagal) | | 1 | |
| *Respiratory, thoracic and mediastinal disorders* | 0 | 3 | 2 |
| Cough | | 1 | |
| Rhinitis NOS | | 2 | 2 |
| *Skin and subcutaneous tissue disorders* | 1 | 0 | 0 |
| Localised skin reaction | 1 | | |
| *Vascular disorders* | 0 | 1 | 0 |
| Hot flushes NOS | | 1 | |

TABLE 6. Summary of Adverse Events–Treatment Emergent Treatment Related

| *Event* | *Placebo* | *High THC* | *CBD:THC* |
|---|---|---|---|
| *No. of subjects with ≥ 1 event* | 5 (20.8%) | 16 (66.7%) | 18 (75.0%) |
| *Eye disorders* | 0 | 1 | 0 |
| Vision blurred | | 1 | |
| *Gastrointestinal disorders* | 1 | 9 | 14 |
| Diarrhoea NOS | | | 1 |
| Glossitis | 1 | | 1 |
| Nausea | | 2 | 2 |
| *Oral discomfort* | | 1 | 1 |
| Oral pain | | 1 | 1 |
| Throat irritation | | 6 | 8 |
| Tongue oedema | | | 1 |
| Vomiting NOS | | | 1 |
| *General disorders and administration site conditions* | 2 | 2 | 1 |
| Feeling of relaxation | 2 | 1 | |
| Lethargy | 2 | 1 | 1 |
| *Injury, poisoning and procedural complications* | 0 | 1 | 2 |
| Drug toxicity NOS | | 1 | 2 |
| *Musculoskeletal and connective tissue disorders* | 0 | 0 | 1 |
| Muscle twitching | | | 1 |
| *Nervous system disorders* | 4 | 10 | 10 |
| Burning sensation NOS | | 1 | 1 |
| Dizziness | 1 | 6 | 2 |
| Dysgeusia | | | 2 |
| Headache NOS | 2 | | 3 |
| Paraesthesia | | 1 | |
| Paraesthesia oral NOS | 1 | 2 | 3 |
| Somnolence | | 3 | 3 |
| Vasovagal attack (LLT syncope vasovagal) | | 1 | |
| *Respiratory, thoracic and mediastinal disorders* | 0 | 1 | 1 |
| Cough | | 1 | |
| Rhinitis NOS | | | 1 |
| *Vascular disorders* | 0 | 1 | 0 |
| Hot flushes NOS | | 1 | |

*Note: treatment related = definitely, probably, possibly related*

TABLE 7. Summary of Number of Subjects Who Experienced at Least One AE per SOC–Treatment Emergent Treatment Related

| *Event* | *Placebo (n = 24)* | *High THC (n = 24)* | *CBD:THC (n = 24)* |
|---|---|---|---|
| No. of subjects with ≥ 1 event | 5 (20.8%) | 16 (66.7%) | 18 (75.0%) |
| Eye disorders | 0 | 1 | 0 |
| Gastrointestinal disorders | 1 | 9 | 14 |
| General disorders and administration site conditions | 2 | 2 | 1 |
| Injury, poisoning and procedural complications | 0 | 1 | 2 |
| Musculoskeletal and connective tissue disorders | 0 | 0 | 1 |
| Nervous system disorders | 4 | 10 | 10 |
| Respiratory, thoracic and mediastinal disorders | 0 | 1 | 1 |
| Vascular disorders | 0 | 1 | 0 |

were no deaths or serious AEs during the study, and no withdrawals attributed to AEs.

### *Clinical Laboratory Evaluation*

All out of range values noted were considered by the Principal Investigator to be "not clinically significant." There were no clinically significant laboratory findings during the study. Several pre- and post-study results were out of the normal range but were not considered clinically significant. There were no statistically significant changes from pre- to post-study in any of the laboratory parameters. There were no notable changes, patterns or trends within the values from pre- and post-study in individual subjects.

### *Vital Signs, Physical Findings and Other Observations Related to Safety*

There were no notable changes in diastolic BP during the study. There was a small transient increase in the mean pulse rate after 15 min during the High THC and CBD:THC periods. After three hours the mean systolic BP decreased by 10.3 mmHg during the High THC period, by 4.4 mmHg in the CBD:THC period, and 5.1 mmHg during the

placebo period. After 12 hours the mean pulse, systolic and diastolic BP values were close to the pre-dose values for all treatments.

No clinically significant changes in physical examination findings were noted from pre- to post-study. Only one change was noted in one subject, which began pre-dose and was not considered to be related to the test treatment. Each subject was asked about their previous medical history at screening. No events were considered to significant in relation to this study. There was no notable trend or pattern in the HR (BPM), PR Interval (msecs), $QT_c$ (msecs), QRS width (msecs) in comparison to placebo. Two subjects had a borderline $QT_c$ after dosing compared to pre-dose values. Subject 115 (CBD:THC period) had an increased $QT_c$ of 41 msec (borderline) after 2 hours, this returned to normal after 12 h. Subject 119 (placebo period) had an increased $QT_c$ of 35 msec (borderline) after 1 h and 33 msec after 12 h. In the opinion of the Investigator both borderline $QT_c$ increases from pre-dose were considered not clinically significant. The ECGs taken during the study were read manually.

### *Safety Conclusions*

The results of this study show that all three test treatments were well tolerated. CBD:THC had the most AEs followed by the THC group and then the placebo group. High THC and CBD:THC had a greater number of subjects who experienced intoxication type AEs and application site type reactions than placebo. The most common overall AE experienced was throat irritation, followed by dizziness, somnolence, oral paraesthesia and then headache. All the events were mild, one required treatment and one event was lost to follow-up.

## *DISCUSSION AND OVERALL CONCLUSIONS*

All three test treatments administered in the study were well tolerated by all subjects. There were no AEs which resulted in any subject withdrawals from the study. Intoxication scores in the study were similarly low for both active treatments and did not appear to be directly related to plasma concentrations of THC and/or 11-hydroxy-THC and intoxication. There were no statistically significant differences in mean $C_{max}$, $t_{1/2}$, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of both THC and 11-hydroxy-THC between the High THC and CBD:THC formulations. THC $T_{max}$ was statistically significantly later (262.7 mins compared with 187.7 mins) following

CBD:THC than High THC ($p = 0.014$) and this was the only statistically significant difference in PK parameters between the treatments. It is possible that the presence of CBD in the CBD:THC formulation delays the absorption of THC.

There was wide inter- and intra-subject variability in PK parameters with up to 10-fold differences in THC AUC between subjects and even greater differences in $C_{max}$. Results suggest that there are no overall statistically significant differences between the PK parameters of High THC and CBD:THC other than a delay in $T_{max}$. Considering the wide inter- and intra-subject variability in PK parameters, including $T_{max}$, this is unlikely to be clinically important in a medication that is self-titrated by the patient.

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