A Phase I, Open Label, Four-Way Crossover Study to Compare the Pharmacokinetic Profiles of a Single Dose of 20 mg of a Cannabis Based Medicine Extract (CBME) Administered on 3 Different Areas of the Buccal Mucosa and to Investigate the Pharmacokinetics of CBME *per Oral* in Healthy Male and Female Volunteers (GWPK0112)

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SUMMARY. This Phase I, open label, four-way crossover study pertains to pharmacokinetic parameters of four cannabis based medicine extracts (CBME). Sublingual, buccal and oro-pharyngeal test treatments

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(GW-1000-02) consisted of 25 mg cannabidiol (CBD) + 25 mg Δ^9-tetrahydrocannabinol (THC) per ml formulated in ethanol (eth):propylene glycol (PG) (50:50), with peppermint flavouring with a 100 µl actuation volume (total dose 10 mg CBD + 10 mg THC in 4 actuations). An oral capsule contained 2.5 mg CBD + 2.5 mg THC sprayed onto granulated lactose and encapsulated in soft gelatin capsules (total dose of 10 mg CBD + 10 mg THC 4 capsules). This study was performed in healthy volunteers in an open label, 4 period, 3-way randomised crossover followed by a non-randomised oral dose using single doses of 20 mg of CBME (10 mg CBD + 10 mg THC). In Periods 1 to 3, the test treatment was administered as a liquid spray according to the randomisation scheme (i.e., sublingually, buccally, oro-pharyngeally). In Period 4 the test treatment was delivered as an oral capsule. There was a six-day washout between each dose.

Primary objectives were to compare the pharmacokinetic profiles of cannabis based medicine extract (CBME) when administered on different areas of the buccal mucosa. Secondary objectives were to investigate the pharmacokinetic profile of CBME when administered as an oral capsule.

Concentrations of THC were higher than the corresponding levels of CBD at most time points. Concentrations of 11-hydroxy-THC exceeded the corresponding concentration of THC at most time points. By 720 min (12 h) post-dose, mean concentrations of each cannabinoid were still above the lower limit of quantification (LLOQ). There was a high degree of inter-subject and intra-subject variability in the plasma concentrations achieved.

T_{max} of CBD and THC occurred earlier following sublingual administration than oro-pharyngeal or buccal although only the difference in T_{max} of CBD compared with buccal was statistically significant. C_{max} of both CBD and THC was greatest following buccal administration although this was not statistically significant. AUC was greatest following oro-pharyngeal and was statistically significantly greater than buccal. The lower bioavailability, as measured by AUC, following buccal administration when compared to the sublingual and oro-pharyngeal routes may be related to the difficulty of spraying onto the inside of the cheek reported during the study and could be due to some loss of spray. Buccal administration of the pump action sublingual spray (PASS) test treatment resulted in a later T_{max} but greater C_{max} when compared to the sublingual and oro-pharyngeal routes. Comparison of the sublingual and oro-pharyngeal routes showed no statistically significant difference in THC or CBD pharmacokinetic parameters other than an earlier T_{max} following sublingual dosing. The oral capsule appeared to show an early T_{max} of both CBD and THC. Mean C_{max} of THC and 11-hydroxy-THC were greater, but in contrast the C_{max} of CBD was lower, than following

the PASS treatments. Relative to THC, the plasma level AUC of 11-hydroxy-THC was proportionally greatest following oral capsules which could be a reflection of greater metabolism by this route. Of the PASS treatments the ratio of 11-hydroxy-THC to THC was greatest following sublingual and least following oro-pharyngeal. There was very wide inter- and to a lesser extent intra-subject variability in pharmacokinetics. Differences in mean values between the routes of administration, even when statistically significant, are small relative to the very wide range of values between subjects. The sublingual and oro-pharyngeal routes of administration appear to have the same pharmacokinetic results. The buccal pharmacokinetic parameters are lower when compared to the sublingual and oro-pharyngeal routes.

A total of 146 adverse events (AEs) occurred in 12 subjects. Two events were classified as moderate (flu-like illness and pharyngeal irritation) and the remaining 144 were classified as mild. All routes of administration were well tolerated by all subjects with no serious AEs and no withdrawals due to AEs.

The overall results indicate that administration of the liquid spray (GW-1000-02) need not be limited to sublingual administration. The oral capsule, has good bioavailability, and provided, as is the case here the formulation is not oil based, may be a viable formulation when self-titration is not necessary. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <http://www.HaworthPress.com> © 2003 by The Haworth Press, Inc. All rights reserved.]*

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 (British Medical Association 1997), and in the UK, oral tinctures of cannabis were prescribed until cannabis was made a Schedule 1 controlled substance in the Misuse of Drugs Act in 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 treat-

ments. 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 Δ^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 (British Medical Association 1997). The MS Society estimated in 1998 that up to 4% (3,400) of UK MS sufferers used cannabis medicinally (House of 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 (GW 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 bene-

fits 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.

SATIVEX (1:1 THC:CBD 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 (Baker, Gough, and Taylor 1983).

SATIVEX was administered as a liquid spray in three different areas of the mouth and 1:1 THC:CBD CBME as an oral capsule. Each formulation contained equal amounts of CBD and THC. GWPK0112 was a Phase I clinical study that aimed to investigate the relative bioavailability of CBME when administered in different areas of the oral mucosa and the absorption and bioavailability of CBME when administered orally. It was also designed to assess safety and tolerability of the test treatments.

Study Preparations

Sublingual, buccal and oro-pharyngeal test treatments (GW-1000-02) consisted of 25 mg cannabidiol (CBD) + 25 mg Δ^9-tetrahydrocannabinol (THC) per ml formulated in ethanol (eth):propylene glycol (PG) (50:50), with peppermint flavouring with a 100 µl actuation volume (total dose 10 mg CBD + 10 mg THC in 4 actuations). An oral capsule contained 2.5 mg CBD + 2.5 mg THC sprayed onto granulated lactose and encapsulated in soft gelatin capsules (total dose of 10 mg CBD + 10 mg THC 4 capsules).

Study Objectives

Primary objectives were to compare the pharmacokinetic profiles of cannabis based medicine extract (CBME) when administered on different areas of the oral mucosa. Secondary objectives were to investigate the pharmacokinetic profile of CBME when administered as an oral capsule and to assess the safety and tolerability of CBME when administered via different areas of the oral mucosa and *per oral* (po).

METHODS

The final study protocol, final Informed Consent Form, and Investigator Brochure were reviewed by PPD Development Clinic Independent Ethics Committee. Unconditional approval to conduct the study was granted on January 10, 2002. Protocol Amendment was approved by the Ethics Committee on February 6, 2002.

The planning and conduct of this study was subject to national laws and was in conformity with the current revision of the Declaration of Helsinki (October 2000, Edinburgh, Scotland), and the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

A written version of the Informed Consent Form was sent to the subjects before attending screening. At the screening visit and prior to any screening procedures being carried out, the Informed Consent Form was presented verbally to the subjects. The Informed Consent Form detailed no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects that they might expect and any risks involved in taking part; subjects were advised that they would be free to withdraw from the study at any time for any reason without prejudice to future care. Subjects were allowed sufficient time and the opportunity to question the Principal Investigator, their General Practitioner or other independent parties to decide whether they wanted to participate in the study. Written Informed Consent was then obtained by means of subject signature, signature of the person who presented Informed Consent and, if different, the Principal Investigator. A copy of the signed Informed Consent Form was given to the subject and the original signed form is retained in the study site files.

This study was conducted at PPD Development Clinic, 72 Hospital Close, Evington, Leicester, LE5 4WW. The plasma concentration analysis was carried out at ABS Laboratories Ltd, Wardalls Grove, Avonley Road, London, SE14 5ER. The Sponsor for this study was GW Pharma Ltd, Alexander House, Forehill, Ely, Cambridgeshire CB7 4ZA. The test treatments used in this study were formulated by G-Pharm Ltd.

Overall Study Design and Plan–Description

The study was an open label, 4 period, 3-way randomised crossover followed by a non-randomised *po* dose using single doses of 20 mg of CBME (10 mg CBD + 10 mg THC). In Periods 1 to 3 the test treatment was administered to subjects as a liquid spray according to the pre-determined randomisation scheme sublingually (Treatment A), buccally

(Treatment B: inside of cheek), oro-pharyngeally (Treatment C: sprayed generally in mouth), and in Period 4, as an oral capsule (Treatment D). Treatments A, B and C were administered as four actuations (sprays) each five minutes apart. The oral capsule was administered *po* as four capsules each five minutes apart. There was a minimum of six days washout between each. The liquid sprays (GW-1000-02) were formulated in 50% ethanol:50% propylene glycol (PG) at a concentration of 25 mg CBD + 25 mg THC/ml, with peppermint flavouring. The 1:1 THC:CBD capsules were produced as 2.5 mg CBD + 2.5 mg THC sprayed onto granulated lactose in soft gelatin capsules.

Twelve healthy subjects (six male and six female) who complied with all the inclusion and exclusion criteria were required to complete the study in its entirety.

Discussion of Study Design

The present route of administration of CBME used to date in patient studies has been limited to sublingual sprays. Due to the limitation of using a small area of the oral cavity there is at least a potential for mucosal tenderness, lesions or other adverse reactions when used chronically. Therefore the different oral mucosal routes of administration were chosen to assess the plasma concentration-time profiles and pharmacokinetic parameters in relation to the sublingual route.

The oral capsule was chosen to make a preliminary assessment of the plasma concentration-time profiles and pharmacokinetic parameters following oral administration. The dose of CBME administered in this study (10 mg CBD + 10 mg THC) was chosen as this is representative of the dosage of the test treatment when used by patients in a self-titrated regime. It is also known to be well tolerated by subjects and produce quantifiable concentrations of cannabinoids in plasma.

GW specified that only subjects with previous experience with the effects of cannabis be included in their Phase I trials to ensure that subjects recognise the effects they may experience as a result of the CBME given. A crossover design was chosen to enable both inter- and intra-subject comparisons of pharmacokinetic data. The study design was open label as blinding was not possible with different routes of administration. A six-day washout ensured all cannabinoids were below the limit of quantification and assisted in the scheduling of the study in the clinical unit.

Inclusion Criteria

For inclusion in the study subjects were required to fulfil all of the following criteria to ensure they were normal healthy subjects and agreed to participate as per the protocol:

i. Healthy and aged between 18 and 50 years
ii. Had a body mass index (BMI) between 19 and 30 kg/m^2
ii. Had given written informed consent
iv. Had experienced the effects of cannabis more than once
v. Agreed to comply with all the study requirements and restrictions
vi. Agreed to use barrier methods of contraception throughout the study and for 3 months post-dose

Subject demographics and habits are noted in Table 1 and 2.

Exclusion Criteria

To ensure they were normal and healthy, subjects were deemed not acceptable for participation in the study if any of the following criteria applied:

i. Had any cardiovascular, haematological, hepatic, gastro-intestinal, renal, pulmonary, neurological or psychiatric disease which in the opinion of the Investigator was significant
ii. Had a history or presence of schizophrenic-type illness
iii. Had a history of drug or alcohol abuse in the past 12 months
iv. Had a history of allergy to cannabis and/or its metabolites
v. Had used cannabis in any form in the 30 days prior to dosing
vi. Had an abnormal blood or urinalysis result at screening which in the opinion of the Investigator was clinically significant
vii. Had a positive drug screen result (including cannabis) at screening
viii. Had a resting blood pressure > 150/95 or < 90/50 mmHg and a pulse < 40 or > 120 b.p.m.
ix. Had taken a course of prescribed medication (with the exception of oral or depot contraceptives) in the 4 weeks prior to dosing
x. Had taken any over-the-counter or prescription medication (with the exception of oral or depot contraceptives) in the 14 days prior to dosing. If currently taking vitamins or paracetamol subjects were asked to discontinue use at screening

xi. Had been hospitalised in the 3 months prior to dosing
xii. Had lost or donated > 400 ml of blood in the 3 months prior to dosing
xiii. Smoked ≥ 5 cigarettes or used ≥ 1/4 ounces of tobacco per day
xiv. Had participated in a clinical trial in the 3 months prior to dosing
xv. Regularly consumed = 28 (males) or = 21 (females) units of alcohol per week
xvi. Was pregnant or lactating at the time of screening
xvii. Planned to become pregnant during or for three months after completion of the study

Study Restrictions

Subjects were required to abstain from the following for the duration of the study:

i. All foods and beverages containing caffeine and alcohol for 24h pre-each dose until the end of each confinement period
ii. Taking any drugs, including drugs of abuse, prescribed and/or over-the-counter medications for the duration of the study
iii. Smoking/using cigarettes/tobacco products during each confinement period
iv. Donating blood or participating in another clinical study in the 3 months after completion of the study

Removal of Subjects from Therapy or Assessment

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.

TABLE 1. Demographic Data

Statistic	*Age (years)*	*Height (m)*	*Weight (kg)*	*BMI (kg/m^2)*
Mean	36.5	1.721	72.38	24.33
Median	36.5	1.73	71.55	24.3
SD	8.38	0.0902	10.785	1.80
Minimum	21	1.58	57.9	21.8
Maximum	48	1.89	98.3	27.5

TABLE 2. Demographics and Habits

Variable	*Frequency*
Sex:	
Male	6
Female	6
Race:	
Caucasian	11
Mixed Race	1
Smoking:	
None	6
≥ 5 cigarettes/day	6
Alcohol:	
None	0
< 14 units/week	10
< 21 units/week	2
Previous cannabis use: Effects experienced more than once	
Yes	12
No	0

Variable	*Frequency*
Drugs of Abuse:	
Negative	12
Positive	0
Pregnancy Test:	
Negative	6
Not Required	0
Contraception:	
Yes	12
No	0
CS Blood/Urine Result:	
Yes	0
No	12

CS = clinically significant

TEST TREATMENTS

Treatments Administered

A total single dose of 10 mg CBD + 10 mg THC was administered sublingually, buccally, oro-pharyngeally or *po* to each of 12 subjects on four occasions. Each single dose (10 mg CBD + 10 mg THC) consisted of a series of four actuations of 100 µl (2.5 mg CBD + 2.5 mg THC per actuation) or four capsules (2.5 mg CBD + 2.5 mg THC per capsule) and each actuation/capsule was administered five minutes apart. Every subject received each of the test treatments once. Each vial and capsule blister pack was labelled with no less than subject number, period number, unit number and expiry date.

For the sublingual, buccal and oro-pharyngeal test treatment (Periods 1-3) subjects were randomised to a dose sequence using a Williams Square Design provided by GW. All subjects received the oral capsule in Period 4. All subjects received a single dose of one test treatment in each period.

Selection of Doses in the Study

The dose given has been previously used in GW studies and has been shown to be both well tolerated and produce quantifiable plasma drug concentrations. The dosing regime was chosen as it has been well tolerated by subjects and in general is a reflection of the dosing regimen used in patient studies when the patients are self-titrating.

Selection and Timing of Dose for Each Subject

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 12 h post-dose without confining the subjects to the clinical unit overnight. 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 open label.

Subjects were required to abstain from taking any medication, over the counter and prescribed for 14 and 28 days, respectively, prior to dosing until completion of the study unless recommended by their General Practitioner. If any subject took concomitant medications during the restriction period it was noted in the CRF and Investigator judgement as to the subjects continued eligibility was made.

Test Treatment Compliance

Subjects were dosed by the Principal Investigator or suitably trained designee. For the sublingual, buccal and oro-pharyngeal routes subjects were instructed to allow each actuation to absorb and not to swallow if possible. For the *po* route, each capsule was placed on the subject's tongue and they were instructed to swallow the capsule using the glass of water (50 ml) provided to wash each capsule down. Following administration of each capsule the person administering the dose checked the subject's mouth to ensure the capsule had been swallowed. The actual time of administration of each actuation/capsule was recorded in the CRF and the dosing procedure was witnessed by a dose verifier. All subjects received all of the scheduled doses and there were no deviations from dosing target times.

STUDY PROCEDURES

Pre-Study Screening

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 were willing to comply with all the study requirements were deemed eligible for participation. The screening procedures comprised the assessments/ measurements shown below.

Demographic Data

The subjects' date of birth, age, sex, race, height, weight, body mass index (BMI), previous cannabis experience, tobacco and alcohol consumption were recorded (Tables 1-2).

Concomitant Medications and Medical History

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. Blood pressure (systolic/diastolic) and pulse were measured after the subject had been seated for no less than two minutes. Oral temperature was also measured. A 12-lead ECG (electrocardiograph) was taken for each subject. At least the following ECG parameters were recorded: HR (heart rate), PR, QT_C and QRS intervals.

Subjects were required to provide a urine sample for routine urinalysis including protein, glucose, ketones, bilirubin, nitrites, blood, urobilinogen, haemoglobin and pH. Microscopy was required to be carried out on any abnormal samples. A pregnancy test was carried out using an HCG Pregnancy Test on all urine samples from female subjects. The samples provided (male and female) were also screened for the drugs of abuse including methadone, benzodiazepines, cocaine, amphetamine, THC, opiates, and barbiturates.

A 4.7 ml blood sample was taken in an ethylenediaminetetraacetic acid (EDTA) blood tube for haematology analysis. A 2.7 ml blood sample was taken in a gel blood tube for routine clinical chemistry analysis.

A blood sample (2.7 ml) was taken in a gel blood tube to screen for the presence of Hepatitis B and/or C.

Pre-Dose Procedures

Subjects were required to arrive at the clinic approximately one hour prior to dosing for each study period. Each subject's health status was updated and pre-dose procedures (health status update, blood pressure and pulse, alcohol and drug of abuse screen and pregnancy test for female subjects) were carried out. Only subjects who complied with the requirements of the study were accepted for inclusion in the study.

Blood Sampling for Plasma CBME Concentration Analysis

Blood samples (4.5 ml) 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 placed in a freezer at −20°C. Blood samples were collected pre-dose and at 15, 30 and 45 min, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8 and 12 h post start of dose.

Plasma concentrations of CBD, THC and 11-hydroxy-THC were measured in each plasma sample. Urine samples were collected in individual 1 L polypropylene containers. Samples were placed in a refrigerator at + 4°C (range of 0 to 10°C) until the end of each collection period. Samples were then pooled by collection period and the total volume recorded. Sub-samples (2 × 20 ml) were retained (stored frozen at −20°C) for analysis and the remainder of the urine discarded. Urine samples were collected for the following time periods: −1 to 0, 0 to 0.5, 0.5 to 1, 1 to 3, 3 to 6 and 6 to 12 h post-dose. Urine concentrations of 11-COOH THC were measured in each urine 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 to 4, 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. The urine sample was required to be negative for all other drugs tested for the subject to be eligible to continue.

Subjects' blood pressure and pulse were measured pre-dose and at 30 min then 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8 and 12 h post start of dosing. A 12-Lead ECG was taken for each subject at the following times: pre-dose and at 30 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8 and 12 h post-dose.

Adverse Events

Subjects' health was monitored continuously throughout the study for Adverse Events (AEs). All AEs were recorded in the CRF. In addition, subjects' health was monitored by asking non-leading questions pre-dose and at the following times post-dose: 15, 30, 45 min, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 12 h post-dose. All AEs were noted and followed to resolution or at the discretion of the Investigator.

Pregnancy Test

A pregnancy test was carried out using an HCG Pregnancy Test for all female subjects on the urine samples provided at check-in for each study period. The test was required to be negative for the subject to continue in the study.

Palatability/Dose Questionnaire

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

Food and Beverages

On study dosing days, subjects were required to abstain from consuming food and beverages for 15 min before the first actuation and 15 min post last actuation (Periods 1-3 only). For Period 4 (capsule dosing) the subjects were not allowed to consume food and beverages for 15 min before dosing and were only allowed to drink the 4×50 ml glasses of water provided for dosing until 15 min after dosing was completed.

Lunch and dinner were provided for the subjects at approximately 4 h and 10 h post-dose, respectively. Snacks, e.g., digestive biscuits, were provided *ad libitum* throughout each confinement period as required.

Subjects were required to drink 100 ml of tap water hourly (with the exception of the food and beverage restriction period) from 1 h pre-dose to 10 h post-dose. Decaffeinated beverages were provided *ad libitum* throughout each confinement period as required.

Check-Out Procedures

After completion of the 12 h study procedures at the end of Periods 1, 2 and 3, and if deemed well enough to leave, subjects were discharged from the clinical unit. Prior to discharge, ongoing AEs were updated and follow up arranged if required. Prior to Period 4 discharge, subjects were required to undergo a physical examination, blood samples were taken for haematology and clinical chemistry analyses and a urine sample taken for urinalysis. In addition 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 Case Report Forms (CRFs) provided by GW for each subject. All data recorded during the study were checked against source data and for compliance with GCP (Good Clinical Practice), internal SOPs (Standard Operating Procedures), working practices and protocol requirements. Monitoring of the study progress and conduct was ongoing throughout the study. Monitoring was conducted by GW Clinical Department staff and was conducted according to GW SOPs. Haematology and clinical chemistry analyses 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 was 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

Data were double entered into approved data tables in Microsoft® Excel 2000 software. Manual checks for missing data and inconsistencies were carried out according to GW's document Data Handling Manual: Manual Checks and queries were raised for any resulting issues. Once the data were clean, i.e., no outstanding queries, then QC checks of 100% of the data for a 10% sample of the patients were conducted in order to make a decision on the acceptability of the data. Any errors were resolved and any error trends across all patients were also corrected. Clinical Quality Audits were carried out.

STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

Statistical and Analytical Plans

With the exception of a SAP being produced prior to carrying out statistical analyses, the statistical analyses were carried out in accordance with the protocol.

Significance Testing and Estimation

The primary analysis was estimation of the pharmacokinetic parameters and thus 95% confidence intervals (CI), in line with current guidelines, are provided for each contrast. Hypothesis testing was secondary in this study. All tests were two-sided.

Pharmacokinetic Analysis

No more than one blood sample per period was omitted for any subject therefore all subjects were considered to be evaluable for pharmacokinetic analysis and were included in the final dataset. All analyses

and summary statistics were carried out and derived using SAS v8. A summary of the mean plasma concentration data is contained in Table 3. Mean pharmacokinetic parameters are contained in Table 4.

Individual plasma concentration-time data and mean profile (mean and standard deviation (SD)) for THC, 11-hydroxy-THC and CBD for each subject were recorded. Plasma concentration-time data were summarised by test treatment group at each time point. Descriptive statistics (number (N), mean, SD, geometric mean, minimum and maximum) were formulated by test treatment for the raw values. Descriptive statistics were calculated for the raw values (N, arithmetic mean, SD, co-efficient of variation (CV%)) and also for the log transformed data (geometric mean, mean of logs and SD of logs).

The pharmacokinetic parameters area under the curve from zero to

TABLE 3. Mean Plasma Concentration Data

Time (min)	*CBD*				*THC*				*11-Hydroxy THC*			
	SL	*Buccal*	*o.p.*	*p.o.*	*SL*	*Buccal*	*o.p.*	*p.o.*	*SL*	*Buccal*	*o.p.*	*p.o.*
0	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00
15	0.06	0.04	0.00	0.06	0.05	0.04	0.01	0.08	0.03	0.02	0.00	0.04
30	0.82	0.26	0.24	1.13	1.17	0.47	0.42	2.94	1.12	0.46	0.38	2.59
45	1.00	0.54	1.18	1.61	1.97	1.21	2.68	4.97	2.71	1.60	1.77	5.82
60	1.30	1.18	1.35	1.44	2.83	2.52	3.20	4.29	4.01	2.71	2.92	6.19
75	1.55	1.20	1.80	1.64	3.41	2.74	4.17	4.23	4.93	3.25	4.02	6.75
90	1.60	1.01	1.76	1.61	3.42	2.47	3.98	3.94	5.34	3.43	4.78	6.50
105	1.73	0.99	1.73	1.41	3.56	2.45	3.71	3.09	5.32	3.78	4.65	5.78
120	1.79	1.03	1.56	1.20	3.92	2.69	3.39	2.57	5.35	3.88	4.36	5.13
135	1.53	1.04	1.57	1.25	3.32	2.57	3.30	2.34	4.71	3.70	4.27	4.71
150	1.36	1.06	1.39	1.07	2.87	2.64	2.96	2.04	4.65	4.00	4.01	4.18
165	1.26	1.08	1.34	1.09	2.48	2.63	2.78	2.02	4.56	4.15	3.90	3.71
180	1.23	1.01	1.31	0.97	2.59	2.34	2.69	1.80	4.55	4.05	3.90	3.59
210	0.96	0.96	0.96	0.66	1.80	2.00	1.98	1.17	3.81	3.37	3.20	2.69
240	0.72	1.34	0.78	0.52	1.27	2.36	1.79	0.88	3.03	3.23	2.97	2.30
270	0.67	1.28	1.02	0.57	1.47	2.04	2.31	0.79	2.81	3.10	3.54	1.91
300	0.55	0.73	0.93	0.35	1.15	1.17	2.01	0.56	2.38	2.32	3.11	1.54
330	0.38	0.50	0.71	0.25	0.79	0.82	1.41	0.39	1.76	1.82	2.40	1.23
360	0.33	0.37	0.51	0.21	0.72	0.64	1.02	0.31	1.62	1.45	2.02	1.08
480	0.22	0.22	0.26	0.13	0.33	0.31	0.40	0.17	0.99	0.88	1.06	0.73
720	0.11	0.11	0.15	0.12	0.13	0.12	0.14	0.13	0.56	0.47	0.56	0.48

SL = sublingual *o.p. = oro-pharyngeal* *p.o. = per oral*
NB. Oral capsule administered in Period 4 (except Subject 010)

TABLE 4. Mean Pharmacokinetic Parameters

Treatment	T_{max} *(min)*	C_{max} *(ng/ml)*	$t_{1/2}$ *(min)*	AUC_{0-t} *(ng/ml.min)*	$AUC_{0-\infty}$ *(ng/ml.min)*
	Mean Pharmacokinetic Parameters for CBD				
Sublingual	98	2.50	86.35	408.53	427.33
Buccal	168	3.02	108.39	384.13	407.79
Oro-Pharyngeal	123	2.61	105.50	469.08	496.98
per oral	76	2.47	65.41	345.68	362.04
	Mean Pharmacokinetic Parameters for THC				
Sublingual	98	5.54	105.70	808.78	837.25
Buccal	144	6.14	80.47	751.23	770.62
Oro-Pharyngeal	134	6.11	81.20	962.68	985.12
per oral	63	6.35	71.71	705.38	724.79
	Mean Pharmacokinetic Parameters for 11-Hydroxy-THC				
Sublingual	95	6.24	128.84	1522.09	1632.46
Buccal	144	6.13	114.34	1293.14	1362.12
Oro-Pharyngeal	144	6.45	125.78	1477.82	1580.33
per oral	81	7.87	100.10	1410.99	1480.39

NB. Oral capsule administered in Period 4 (except Subject 010)

infinity ($AUC_{0-\infty}$), area under the curve from zero to t (AUC_{0-t}) and maximum concentration (C_{max}) were log transformed prior to analysis and analysed using the first three periods only. The analysis of variance (ANOVA) model included terms for subject, period and treatment. Least squares means for the treatments were transformed back to the original scale and presented as geometric means. The differences for each of the three pairwise contrasts were exponentiated to express them as ratios of geometric means with 95% confidence intervals.

Time to maximum concentration (T_{max}) and half-life ($t_{1/2}$) were analysed and transformed using the same model as above. The elimination rate constant (K_{el}) is presented descriptively only. Oral capsule data are presented descriptively.

No statistical comparisons were carried out on the urine data.

SAFETY ANALYSIS

Adverse Events

All Adverse Events were coded by Medical Dictionary of Regulatory Activities (MedDRA) and presented by System Organ Class (SOC) and

Preferred Term (PT). For each table, the distribution (n and %) of subjects are presented. The following summary tables were produced: overview summary of treatment-related Adverse Events and all causality Adverse Events.

Clinical Laboratory Tests

For each of the haematology and clinical chemistry parameters, descriptive statistics (N, mean, SD, median, minimum and maximum) were calculated and summarised by treatment group at screening and post-study. In addition, descriptive statistics were calculated and summarised for the change from screening.

Listings of clinical chemistry parameters at screening and post-study are presented in Table 5. Abnormal values were designated as H (high) or L (low) in the individual data listings based on the Normal Labora-

TABLE 5. Mean Clinical Chemistry Data

Variable	*Mean pre-study (SD) n = 12*	*Mean post-study (SD) n = 12*	*Difference (SD) n = 12*
AST (iu/l)	20.4 (4.60)	16.2 (3.41)	−4.3 (3.14)
ALT (iu/l)	17.4 (7.91)	15.2 (7.17)	−2.3 (2.34)
Alk phosph. (iu/l)	66.4 (14.64)	61.7 (20.11)	−4.8 (15.26)
GGT (iu/l)	19.2 (6.71)	14.5 (4.70)	−4.7 (3.55)
Total Bilirubin (µmol/l)	11.4 (5.52)	6.0 (2.86)	−5.4 (4.19)
Albumin (g/l)	44.7 (2.77)	38.9 (2.27)	−5.8 (3.93)
Total Protein (g/l)	71.0 (5.06)	63.9 (3.92)	−7.1 (5.12)
Urea (mmol/l)	4.78 (1.011)	4.55 (0.922)	−0.23 (0.916)
Creatinine (µmol/l)	79.3 (10.01)	87.8 (10.08)	8.4 (7.63)
Adjusted Calcium (mmol/l)	2.247 (0.0785)	2.351 (0.1435)	0.104 (0.0914)
Sodium (mmol/l)	137.8 (1.19)	138.3 (1.22)	0.4 (1.24)
Potassium (mmol/l)	4.08 (0.299)	4.11 (0.178)	0.03 (0.281)

tory Reference Ranges. Shift tables were constructed to determine the categorical shifts from screening to post-study. For vital signs and/or blood pressure and pulse descriptive statistics (N, mean, SD, median, minimum and maximum) were calculated and summarised at each time point by treatment group. In addition, the calculations were performed for the absolute change from pre-dose.

For each of the ECG parameters (heart rate, PR interval, QT_c interval and QRS width), descriptive statistics (N, mean, SD, median, minimum and maximum) were calculated and summarised at each time point by treatment group. In addition, the calculations were performed for the absolute change from pre-dose.

No concomitant medications were taken by any subjects throughout the study. No formal sample size calculation was carried out for this study. Only one minor change to the planned analyses occurred; the planned CI for statistical analyses (90%) was changed to 95%.

Study Subjects

Six healthy male and six healthy female subjects were required to complete the study in its entirety (see demographic data). Six male and six female subjects were randomised and all of those subjects completed the study. No subjects withdrew from the study and no replacements were required.

Protocol Deviations

The following protocol deviations which occurred during the study required investigator judgement:

1. A 4.7 ml blood sample was taken in a gel blood tube blood from each subject at pre-study screening to screen for the presence of Hepatitis B and/or C. The blood sampling for this analysis and results were retained with the individual subject CRFs.
2. Subject 010 was ill for dosing Period 3, however, did wish to continue in the study and a decision was made to delay the subject by one week. The dose to be received in Period 4 would have expired prior to the dosing date therefore the doses for Period 3 and 4 were reversed so that the subject received the oral capsule in Period 3. The actual dates of dosing for each period were recorded in the CRF.

3. A SAP was not produced prior to the statistical analyses being carried out. Statistical analyses were carried as detailed in this report.

The protocol deviations noted are not considered to affect the integrity of the study.

Plasma and Urine Concentration and Plasma Pharmacokinetic Evaluation

All twelve subjects (001 to 012) who were randomised in the study were included in the data analysis. All subjects included in the study complied with all demographic and baseline requirements for inclusion.

Measurements of Compliance

Each test treatment was administered by suitably trained study site clinical staff. No deviations to the dosing regimen were noted for any subject through out the study. The site clinical staff reported a slight difficulty in aiming the buccal dose onto the inside of the cheek, however, each dose was administered with no deviations.

INDIVIDUAL PLASMA CONCENTRATION DATA AND PHARMACOKINETIC RESULTS

Analysis of Plasma Concentration Data

Plasma samples were analysed for CBD, THC and 11-hydroxy-THC according to the analytical protocol. Plasma concentration results were produced in tabular form and concentration-time graphs were produced from these data. The LLOQ for this study was 0.1 ng/ml. Data below the LLOQ are presented as < 0.1 and the actual value measured is presented in parentheses. The actual values measured were used when creating graphs.

The mean values listed in Table 3 show that CBD, THC and 11-hydroxy-THC were all detectable in plasma at around 15-30 min after dosing. Plasma concentrations generally increased to a peak between 45 and 120 min, although following buccal dosing the mean peak of CBD was later, and thereafter diminished though low concentrations were still detectable 720 min after dosing.

Plasma levels of THC (Figure 1) exceeded the corresponding level of

CBD (Figure 2) at almost all time points by a factor of approximately 2 except early and late in the sampling schedule when concentrations of both were low. Approximately 60 min after dosing plasma levels of THC were exceeded by the levels of 11-hydroxy-THC, its principal metabolite, except following oro-pharyngeal dosing when this was delayed and did not occur until after 90 min (Figure 3).

The SDs for the mean plasma concentrations of each cannabinoid, indicate a relatively high inter-subject variability in the rate and extent of absorption (Figures 4-16). This inter-subject variation in the extent of absorption does not seem to be consistently predictable from one treatment to another due to additional intra-subject variability.

Analysis of Urine Concentration Data

Urine samples were analysed for 11-COOH THC according to the analytical protocol. Mean urine concentrations are listed in Table 6 and summarised graphically in Figure 17. The LLOQ (lower limit of quantification) for this study was 0.5 ng/ml. Data below the LLOQ are presented as < 0.5 and the actual value measured is presented in parentheses. Urine samples were collected in polypropylene containers and the binding of cannabinoids to this material is unknown. Therefore the

FIGURE 1. GWPK0112 Mean CBME THC PK Data Following Administration of CBME via Different Routes

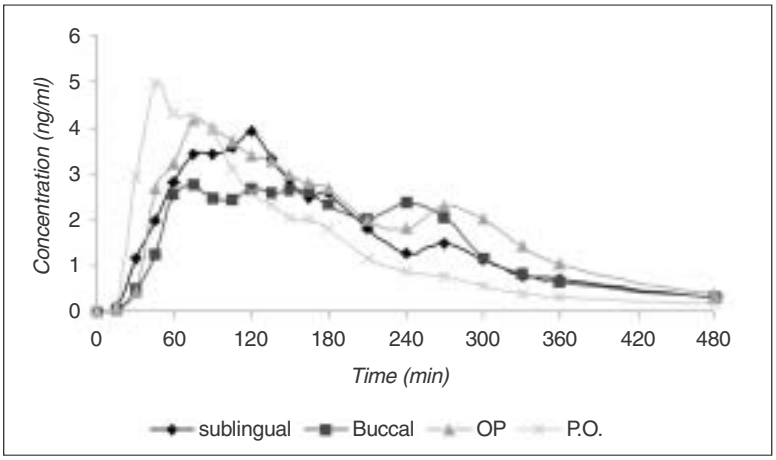


FIGURE 2. GWPK0112 Mean CBME CBD PK Data Following Administration of CBME via Different Routes

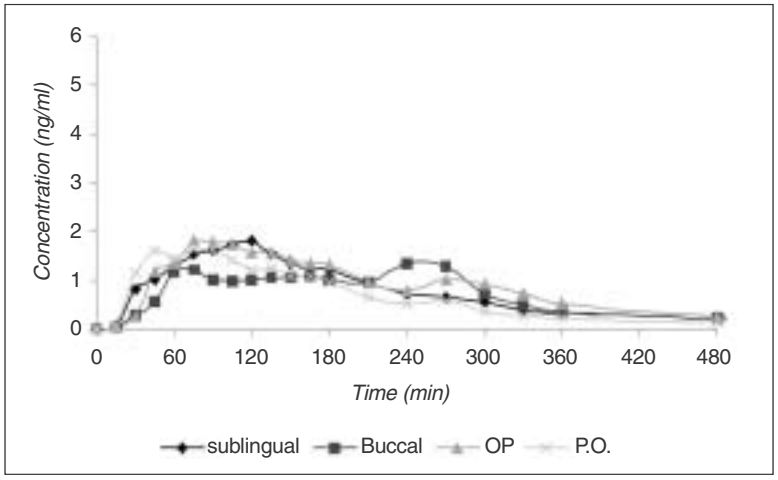


FIGURE 3. GWPK0112 Mean CBME 11-Hydroxy-THC PK Data Following Administration of CBME via Different Routes

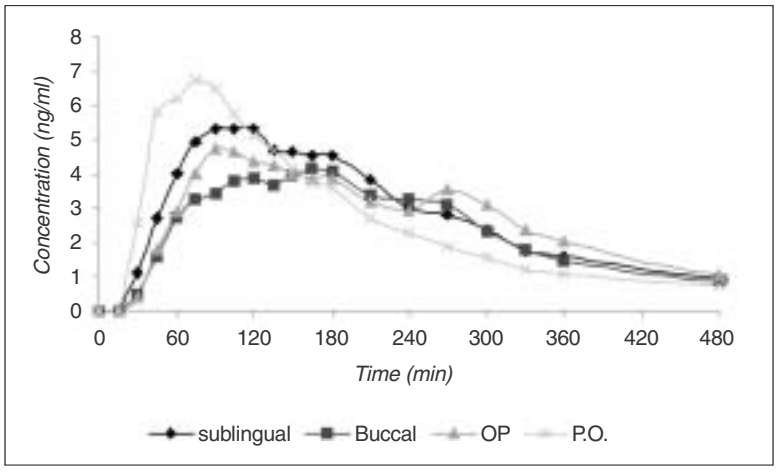


FIGURE 4. GWPK0112 Mean CBME THC PK Data Following Sublingual Administration

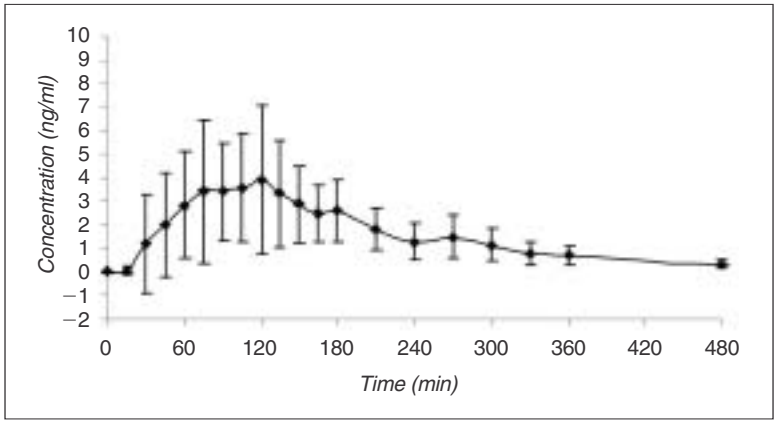
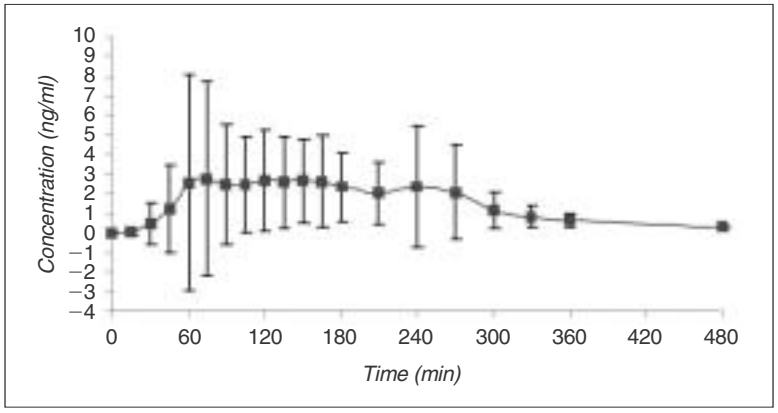


FIGURE 5. GWPK0112 Mean CBME THC PK Data Following Buccal Administration



reliability of the data is not known. Pre-dose, some subjects had quantifiable amounts of 11-COOH THC in urine. Mean pre-dose concentrations were: 0.21, 0.27, 0.36 and 0.91 ng/ml in the urine samples collected in the hour prior to sublingual, buccal, oro-pharyngeal or oral capsule dosing, respectively.

FIGURE 6. GWPK0112 Mean CBME THC PK Data Following Oro-Pharyngeal Administration

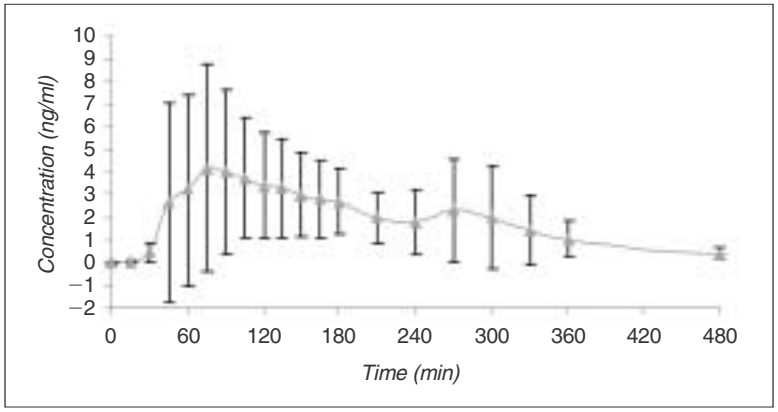
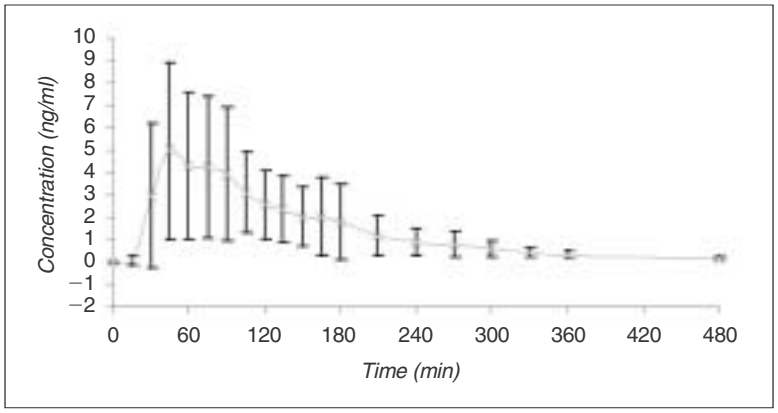


FIGURE 7. GWPK0112 Mean CBME THC PK Data Following P.O. Administration (Capsule)



No unchanged CBD or THC were detected in urine following administration of each test treatment. A metabolite of THC (11-COOH THC) was detected and was quantified. Following each treatment the excretion of 11-COOH THC was low up to one hour after dosing, increased markedly during the 1-3 h post-dose period and increased further during

FIGURE 8. GWPK0112 Mean CBME Plasma Concentration Results Following Sublingual Administration (Subjects 1-12)

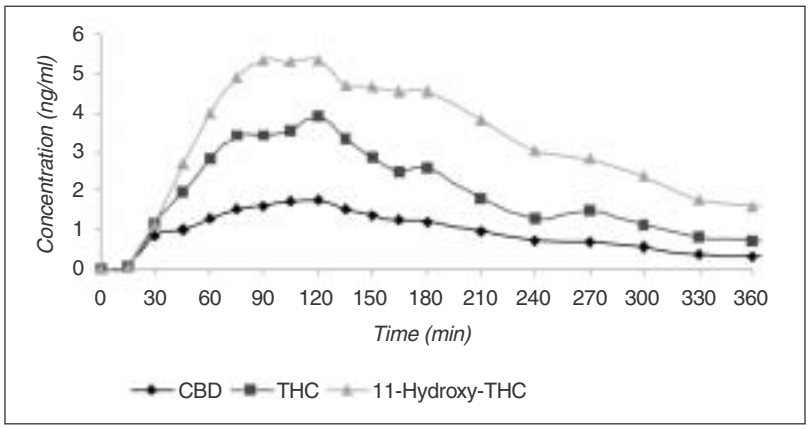
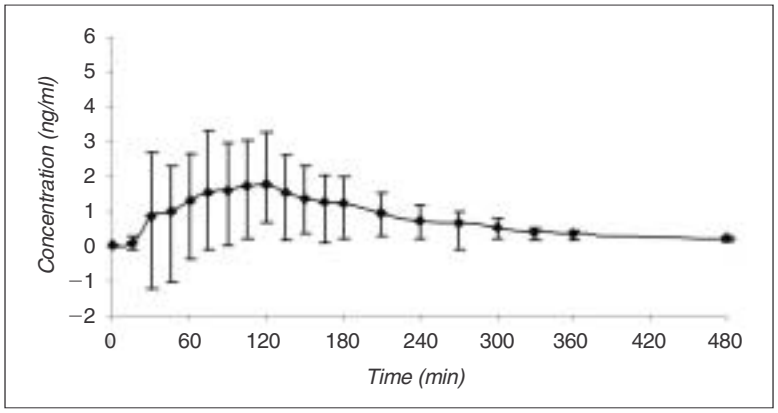


FIGURE 9. GWPK0112 Mean CBME CBD PK Data Following Sublingual Administration



the 3-6 h period before declining again during the 6-12 h post-dose period (Table 6). All four test treatments showed a similar pattern. The highest total mean excretion apparently was achieved following administration of the oral capsule followed by the sublingual spray, buccal spray and finally oro-pharyngeal spray. However, as excretion of 11-hydroxy-THC was apparently not complete after the 6-12 h collection period, these findings should be interpreted with caution.

FIGURE 10. GWPK0112 Mean CBME CBD PK Data Following Buccal Administration

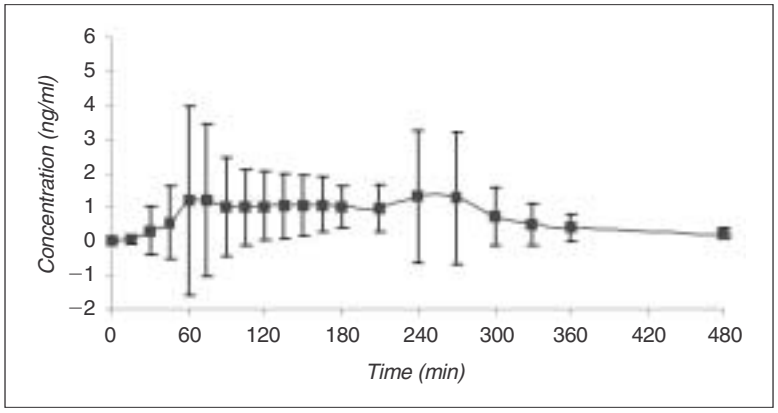
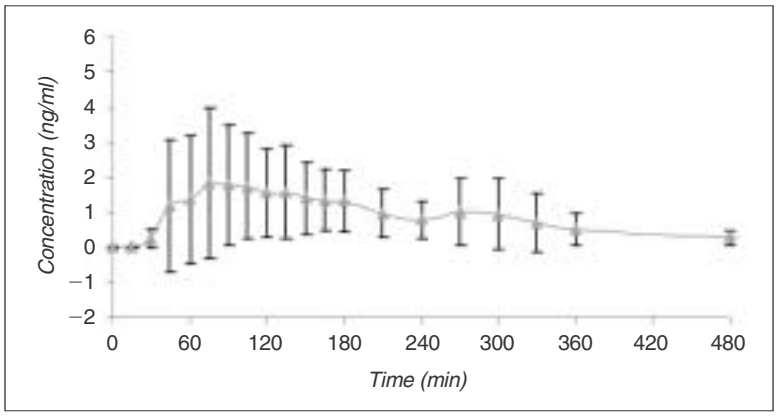


FIGURE 11. GWPK0112 Mean CBME CBD PK Data Following Oro-Pharyngeal Administration



Analysis of Pharmacokinetic Parameters

Pharmacokinetic parameters were calculated using WinNonlin® Professional 3.1. The model used was a non-compartmental, linear trapezoidal analysis. Values below the LLOQ are not considered reliable and therefore were not used when calculating PK parameters. Mean pharmacokinetic values are presented in Table 4 and displayed in the graphs.

FIGURE 12. GWPK0112 Mean CBME CBD PK Data Following P.O. Administration (Capsule)

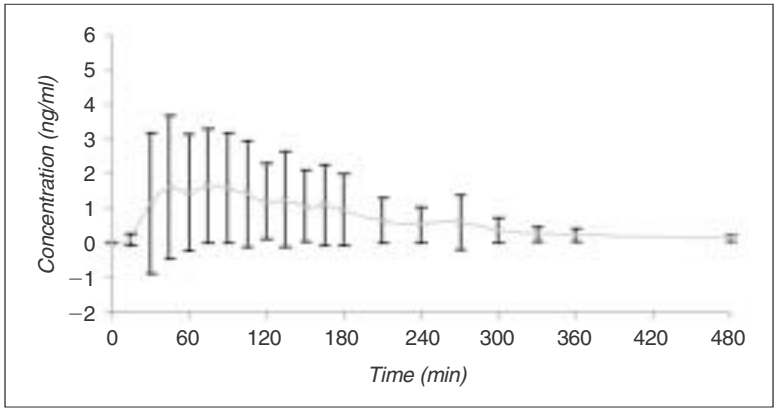
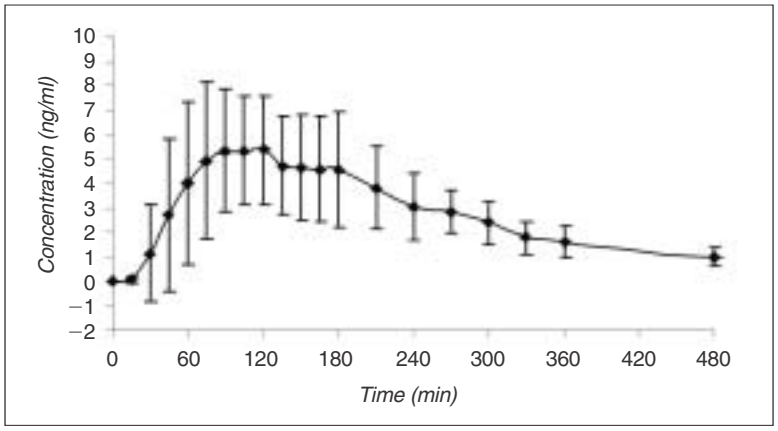


FIGURE 13. GWPK0112 Mean CBME 11-Hydroxy THC PK Data Following Sublingual Administration



Analysis of PASS Sublingual, Buccal and Oro-Pharyngeal Pharmacokinetic Parameters

Mean T_{max} of both THC (Table 7) and CBD (Table 8) occurred earlier following sublingual administration (98 min) than oro-pharyngeal (123 min CBD, 134 min THC) (Tables 9 and 10) or buccal (168 min

FIGURE 14. GWPK0112 Mean CBME 11-Hydroxy-THC PK Data Following Buccal Administration

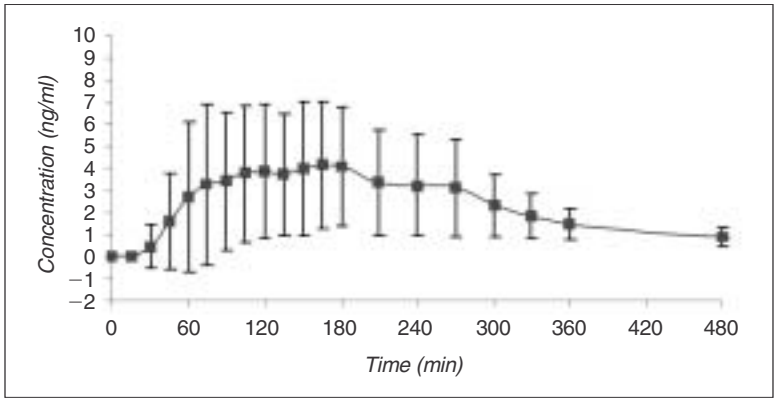
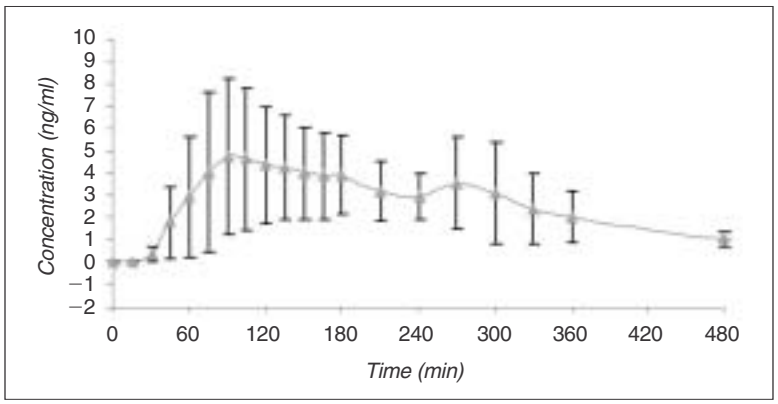


FIGURE 15. GWPK0112 Mean CBME 11-Hydroxy-THC PK Data Following Oro-Pharyngeal Administration



CBD, 144 min THC) (Tables 11 and 12) though only the difference in CBD T_{max} between buccal and sublingual administration reached statistical significance ($p = 0.0059$). C_{max} of both THC and CBD was greatest following buccal administration then oro-pharyngeal and finally sublingual, although none of the differences reached statistical significance. $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of both THC and CBD were greatest following oro-pharyngeal administration followed by sublingual then

FIGURE 16. GWPK0112 Mean CBME 11-Hydroxy-THC PK Data Following P.O. Administration (Capsule)

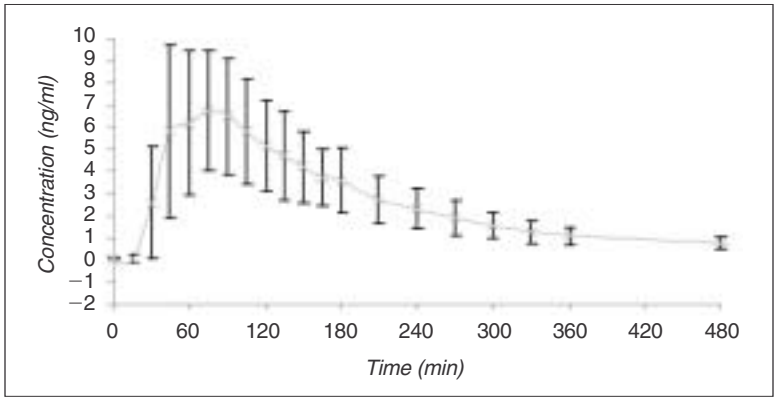


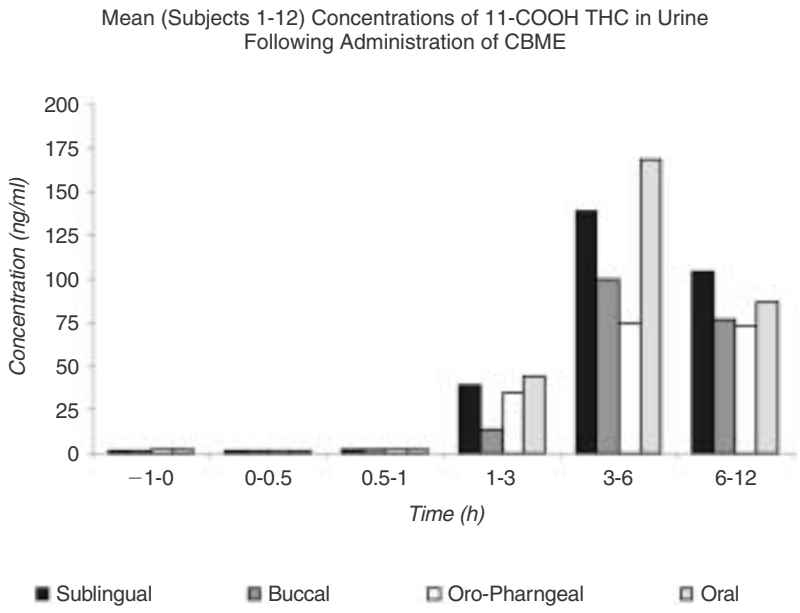
TABLE 6. Mean Excretion of 11-COOH THC in Urine (ng/ml) per Time Period

Time Period (h)	*Test Treatment*			
	Sublingual	*Buccal*	*Oro-Pharyngeal*	*Oral Capsule*
−1-0	0.21	0.27	0.36	0.91
0-0.5	0.05	0.20	0.32	0.29
0.5-1	1.10	0.75	0.89	1.61
1-3	38.45	13.55	34.53	44.17
3-6	139.33	99.29	74.40	168.84
6-12	104.08	75.97	73.30	87.12
Total	283.22	190.03	183.8	302.94

buccal dosing. The differences in $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of THC between oro-pharyngeal and buccal dosing were statistically significant ($AUC_{0\text{-}t}$ $p = 0.0024$ and $AUC_{0\text{-}\infty}$ $p = 0.0018$). The bioavailability of THC was approximately twice that of CBD irrespective of the site of application.

There were significant differences in the pharmacokinetic parameters of 11-hydroxy-THC between the different administrations. T_{max} of 11-hydroxy-THC occurred statistically significantly earlier (95 min) after sublingual dosing (Table 13) than buccal (144 min, $p = 0.038$) (Table 14) or oro-pharyngeal (144 min, $p = 0.038$) (Table 15). There were no statistically significant differences in C_{max} of 11-hydroxy-THC between treatments. $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were significantly lower after

FIGURE 17. Mean Urine 11-COOH THC Concentrations (ng/ml) in Urine Following Administration of Each Test Treatment



NB. Mean data taken from Table 3

TABLE 7. Summary of Plasma THC Pharmacokinetic Parameters–PASS Sublingual

Statistic	$AUC_{0-\infty}$ *(ng/ml ·min)*	AUC_{0-t} *(ng/ml ·min)*	C_{max} *(ng/ml)*	T_{max} *(min)*	$t_{1/2}$ *(min)*
N	12	12	12	12	12
Arithmetic mean	837.3	808.8	5.54	97.5	105.7
Geometric mean	772.5	745	4.64	-	-
Minimum	429.3	406.9	1.14	60	45.4
Maximum	1857.5	1812	12.13	180	193.7
SD	387.34	378.36	3.346	35.32	39.743
CV%	46.3	46.8	60.4	36.2	37.6
Log transformed:					
Mean	6.6496	6.6134	1.5349	-	-
SD	0.4049	0.4087	0.651	-	-

TABLE 8. Summary of Plasma CBD Pharmacokinetic Parameters–PASS Sublingual

Statistic	$AUC_{0-\infty}$ *(ng/ml ·min)*	AUC_{0-t} *(ng/ml ·min)*	C_{max} *(ng/ml)*	T_{max} *(min)*	$t_{1/2}$ *(min)*
N	12	12	12	12	12
Arithmetic mean	427.3	408.5	2.5	97.5	86.35
Geometric mean	370.1	344.3	1.87	-	-
Minimum	137.5	93.8	0.27	45	44.2
Maximum	1106.4	1083.8	6.55	180	201.6
SD	258.86	259.86	1.8281	40.7	47.18
CV%	60.6	63.6	73.2	41.7	54.6
Log transformed:					
Mean	5.9137	5.8414	0.6286	-	-
SD	0.5537	0.625	0.866	-	-

TABLE 9. Summary of Plasma THC Pharmacokinetic Parameters–PASS Oro-Pharyngeal

Statistic	$AUC_{0-\infty}$ *(ng/ml ·min)*	AUC_{0-t} *(ng/ml ·min)*	C_{max} *(ng/ml)*	T_{max} *(min)*	$t_{1/2}$ *(min)*
N	12	12	12	12	12
Arithmetic mean	985.1	962.7	6.11	133.8	81.2
Geometric mean	897.7	874.2	5.06	-	-
Minimum	413.3	404.4	1.94	45	41.8
Maximum	1772.1	1758.3	15.68	300	162.5
SD	440.27	439.99	3.998	91.23	30.838
CV%	44.7	45.7	65.5	68.2	38
Log transformed:					
Mean	6.7998	6.7733	1.621	-	-
SD	0.4545	0.4618	0.648	-	-

TABLE 10. Summary of Plasma CBD Pharmacokinetic Parameters–PASS Oro-Pharyngeal

Statistic	$AUC_{0-\infty}$ *(ng/ml ·min)*	AUC_{0-t} *(ng/ml ·min)*	C_{max} *(ng/ml)*	T_{max} *(min)*	$t_{1/2}$ *(min)*
N	12	12	12	12	12
Arithmetic mean	497	469.1	2.61	122.5	105.5
Geometric mean	417.3	387.8	2.01	-	-
Minimum	128.2	109.4	0.41	45	41.4
Maximum	1286.8	1201.3	6.36	300	186.1
SD	319.34	307.78	1.907	67.94	47.879
CV%	64.3	65.6	73	55.5	45.4
Log transformed:					
Mean	6.0337	5.9606	0.7004	-	-
SD	0.6238	0.657	0.7923	-	-

TABLE 11. Summary of Plasma THC Pharmacokinetic Parameters–PASS Buccal

Statistic	$AUC_{0-\infty}$ *(ng/ml ·min)*	AUC_{0-t} *(ng/ml ·min)*	C_{max} *(ng/ml)*	T_{max} *(min)*	$t_{1/2}$ *(min)*
N	12	12	12	12	12
Arithmetic mean	770.6	751.2	6.14	143.8	80.47
Geometric mean	664.6	640.4	4.39	-	-
Minimum	233.6	225.3	0.88	60	44.6
Maximum	1666.9	1656	19.78	270	168.4
SD	427.22	431.19	5.367	65.06	38.807
CV%	55.4	57.4	87.4	45.3	48.2
Log transformed:					
Mean	6.4992	6.4621	1.4791	-	-
SD	0.5852	0.6081	0.8827	-	-

TABLE 12. Summary of Plasma CBD Pharmacokinetic Parameters–PASS Buccal

Statistic	$AUC_{0-\infty}$ *(ng/ml ·min)*	AUC_{0-t} *(ng/ml ·min)*	C_{max} *(ng/ml)*	T_{max} *(min)*	$t_{1/2}$ *(min)*
N	12	12	12	12	12
Arithmetic mean	407.8	384.1	3.02	167.5	108.39
Geometric mean	328.1	287.9	1.82	-	-
Minimum	100.5	80.4	0.29	60	38.2
Maximum	862.7	852.4	9.91	270	451.4
SD	267.8	277.34	3.1478	78.81	122.936
CV%	65.7	72.2	104.1	47.1	113.4
Log transformed:					
Mean	5.7932	5.6625	0.5996	-	-
SD	0.7146	0.8429	1.0925	-	-

TABLE 13. Summary of Plasma 11-Hydroxy-THC Pharmacokinetic Parameters–PASS Sublingual

Statistic	$AUC_{0-\infty}$ *(ng/ml ·min)*	AUC_{0-t} *(ng/ml ·min)*	C_{max} *(ng/ml)*	T_{max} *(min)*	$t_{1/2}$ *(min)*
N	12	12	12	12	12
Arithmetic mean	1632.5	1522.1	6.24	95	128.84
Geometric mean	1508.2	1410.6	5.7	-	-
Minimum	635.7	621.6	2.67	60	54.3
Maximum	3058.3	2906.3	10.77	165	270.3
SD	687.19	638.68	2.744	26.63	59.252
CV%	42.1	42	43.9	28	46
Log transformed:					
Mean	7.3187	7.2518	1.7409	-	-
SD	0.4198	0.4079	0.45	-	-

TABLE 14. Summary of Plasma 11-Hydroxy-THC Pharmacokinetic Parameters–PASS Buccal

Statistic	*$AUC_{0-\infty}$ (ng/ml ·min)*	*AUC_{0-t} (ng/ml ·min)*	*C_{max} (ng/ml)*	*T_{max} (min)*	*$t_{1/2}$ (min)*
N	12	12	12	12	12
Arithmetic mean	1362.1	1293.2	6.13	143.8	114.34
Geometric mean	1191.5	1123.2	5.48	-	-
Minimum	357.1	345.1	1.83	60	66.4
Maximum	3308.9	3152.3	11.25	270	323.5
SD	753.7	728.83	2.878	69.91	74.866
CV%	55.3	56.4	46.9	48.6	65.5
Log transformed:					
Mean	7.083	7.0239	1.7002	-	-
SD	0.5582	0.574	0.524	-	-

TABLE 15. Summary of Plasma 11-Hydroxy-THC Pharmacokinetic Parameters–PASS Oro-Pharyngeal

Statistic	*$AUC_{0-\infty}$ (ng/ml ·min)*	*AUC_{0-t} (ng/ml ·min)*	*C_{max} (ng/ml)*	*T_{max} (min)*	*$t_{1/2}$ (min)*
N	12	12	12	12	12
Arithmetic mean	1580.3	1477.8	6.45	143.8	125.78
Geometric mean	1520.1	1420.6	5.94	-	-
Minimum	737	688.7	2.95	75	59
Maximum	2483.7	2379.3	13.49	300	260.8
SD	440.08	420.39	2.905	73.05	56.496
CV%	27.8	28.4	45.1	50.8	44.9
Log transformed:					
Mean	7.3265	7.2588	1.7815	-	-
SD	0.3019	0.3032	0.416	-	-

buccal than either sublingual or oro-pharyngeal dosing. The ratios of AUC_{0-t} of 11-hydroxy-THC to THC were 1.5, 1.7 and 1.9:1 (calculated from Table 4) following oro-pharyngeal, buccal and sublingual dosing, respectively.

Inter-subject variability in pharmacokinetics was considerable with CV% of the order of 45 to 70% in AUC, 38 to 68% in T_{max} and 44 to 113% in C_{max} (calculated from Table 4). Following each treatment differences between the lowest and highest C_{max} values observed in individual subjects ranged from 8 to 46-fold, with the range being generally greater for CBD than THC. The difference between lowest and highest AUC_{0-t} was less, being of the order of 11-fold for CBD after all formulations and 4 to 7-fold for THC. While some individuals tended to show

consistency in high or low AUC or C_{max} values across all treatments, others showed considerable intra-subject variability.

Analysis of Oral Capsule Pharmacokinetic Parameters

Following administration of the oral capsules the mean T_{max} of CBD was 76 min (Table 16) and for THC 63 min (Table 17). The C_{max} of CBD was 2.47 ng/ml and C_{max} of THC was 6.35 ng/ml. T_{max} of CBD, THC and 11-hydroxy-THC (Table 18) occurred earlier following dosing with oral capsules than dosing with sublingual buccal or oro-pharyngeal sprays.

TABLE 16. Summary of Plasma CBD Pharmacokinetic Parameters–Oral Capsule

Statistic	$AUC_{0-\infty}$ *(ng/ml ·min)*	AUC_{0-t} *(ng/ml ·min)*	C_{max} *(ng/ml)*	T_{max} *(min)*	$t_{1/2}$ *(min)*
N	12	12	12	12	12
Arithmetic mean	362	345.7	2.47	76.3	65.41
Geometric mean	259.1	240.8	1.72	-	-
Minimum	79.1	67.3	0.47	30	22.9
Maximum	932.8	921.1	7.55	180	108.5
SD	298.28	296.28	2.233	50.55	27.58
CV%	82.4	85.7	90.3	66.3	42.2
Log transformed:					
Mean	5.5571	5.4838	0.5406	-	-
SD	0.8779	0.9129	0.8964	-	-

TABLE 17. Summary of Plasma THC Pharmacokinetic Parameters–Oral Capsule

Statistic	$AUC_{0-\infty}$ *(ng/ml ·min)*	AUC_{0-t} *(ng/ml ·min)*	C_{max} *(ng/ml)*	T_{max} *(min)*	$t_{1/2}$ *(min)*
N	12	12	12	12	12
Arithmetic mean	724.8	705.4	6.35	62.5	71.72
Geometric mean	656.2	635	5.79	-	-
Minimum	366	357.8	3.04	30	36.8
Maximum	1744.4	1731.8	14.55	165	134.1
SD	375.66	377.07	3.122	38.82	25.583
CV%	51.8	53.5	49.2	62.1	35.7
Log transformed:					
Mean	6.4864	6.4537	1.7564	-	-
SD	0.45	0.4619	0.4327	-	-

TABLE 18. Summary of Plasma 11-Hydroxy-THC Pharmacokinetic Parameters–Oral Capsule

Statistic	*$AUC_{0-\infty}$ (ng/ml ·min)*	*AUC_{0-t} (ng/ml ·min)*	*C_{max} (ng/ml)*	*T_{max} (min)*	*$t_{1/2}$ (min)*
N	12	12	12	12	12
Arithmetic mean	1480.4	1411	7.87	81.3	100.1
Geometric mean	1394.5	1331.6	7.4	-	-
Minimum	623.6	608.9	4.79	45	67.1
Maximum	2470.5	2389.4	13.64	180	132.4
SD	515.87	487.29	2.958	38.09	17.69
CV%	34.8	34.5	37.6	46.9	17.7
Log transformed:					
Mean	7.2403	7.1941	2.0021	-	-
SD	0.3724	0.3655	0.3585	-	-

Mean AUC_{0-t} and $AUC_{0-\infty}$ of CBD (345.68 and 362.04 ng/ml.min, respectively) were lower, whereas the mean AUC_{0-t} and $AUC_{0-\infty}$ of THC (705.38 and 724.79 ng/ml.min, respectively) were greater following dosing with oral capsules than with the sublingual, buccal or oro-pharyngeal sprays. The bioavailability of THC was approximately twice that of CBD. The mean T_{max} of 11-hydroxy-THC (81 min) was a little later than that of CBD or THC, though still earlier than following dosing with sublingual buccal or oro-pharyngeal sprays. The C_{max} (7.87 ng/ml) for 11-hydroxy-THC was greater than that of THC. Mean AUC_{0-t} and $AUC_{0-\infty}$ (1410.99 and 1480.39 ng/ml.min, respectively) were twice the corresponding values for THC.

Analysis of Safety Parameters

For each of the blood pressure and pulse parameters descriptive statistics (n, mean, SD, median, minimum and maximum) were calculated and summarised at each time point by treatment group. In addition, the calculations were performed for the absolute change from pre-dose.

For each of the ECG parameters (heart rate, PR interval, QT_c interval and QRS width), descriptive statistics (N, mean, SD, median, minimum and maximum) were calculated and summarised at each time point by treatment group. In addition, the calculations were performed for the absolute change from pre-dose. For QT_c, absolute values and changes from pre-dose were categorised as borderline, normal, prolonged according to CPMP guidelines.

Statistical/Analytical Issues

There were no specific statistical or analytical issues in this study.

Plasma Concentration Conclusions

Mean data indicate an almost simultaneous appearance of all three cannabinoids in plasma at 30 minutes after dosing, though in individuals there was considerable variability in the time to first appearance of the cannabinoids (range 15-105 minutes).

Concentrations of THC were higher than the corresponding levels of CBD at most time points. Concentrations of 11-hydroxy-THC exceeded the corresponding concentration of THC at most time points after 45 min. By 720 min (12 h) post-dose, mean concentrations of each cannabinoid were still above the LLOQ.

There was a high degree of inter-subject and intra-subject variability in the plasma concentrations achieved.

Urine Concentration Conclusions

No statistical analyses were carried out on the urine data. Urine samples were collected in polypropylene containers and due to the affinity of cannabinoids to plastic, the accuracy of the urine data is not known. 11-COOH THC (a metabolite of THC) was detected in urine throughout the sampling period in quantifiable amounts.

The excretion of 11-COOH THC began within the first 0.5 to 1 hour after dosing, peaked during the 3-6 h collection period and thereafter decreased. Administration of the oral capsules resulted in resulted in the greatest total concentrations of 11-COOH THC excreted, followed by dosing sublingually and the buccal and oro-pharyngeal routes showed approximately the same extent of excretion of 11-COOH THC throughout the sampling period.

Pharmacokinetic Conclusions

T_{max} of CBD and THC occurred earlier following sublingual administration than oro-pharyngeal or buccal although only the difference in T_{max} of CBD compared with buccal was statistically significant.

C_{max} of both CBD and THC for the PASS test treatments was greatest following buccal administration although this was not statistically significant. AUC was greatest following oro-pharyngeal administration

and was statistically significantly greater than following buccal administration. The lower bioavailability, as measured by AUC, following buccal administration when compared to the sublingual and oro-pharyngeal routes may be related to the difficulty of spraying onto the inside of the cheek reported during the study. Buccal administration of the PASS test treatment resulted in a later T_{max} but greater C_{max} when compared to the sublingual and oro-pharyngeal routes.

Comparison of the sublingual and oro-pharyngeal routes showed no statistically significant difference in THC or CBD pharmacokinetic parameters measured.

Pharmacokinetic parameters following administration of the oral capsule were not statistically compared to the other routes as this was an early investigation into the safety and tolerability of this dose route. However, this dosage form and route of administration appeared to show an early T_{max} of both CBD and THC. Mean C_{max} of THC and 11-hydroxy-THC were greater, but in contrast the C_{max} of CBD was lower, than following the PASS treatments.

Relative to THC, the plasma level AUC of 11-hydroxy-THC was proportionally greatest following dosing with the oral capsules which could be a reflection of greater metabolism by this route. Of the PASS treatments the ratio of 11-hydroxy-THC to THC was greatest following sublingual and least following oro-pharyngeal dosing.

The oral capsule has good bioavailability, and provided, as is the case here, the formulation is not oil based, may be a viable formulation when self-titration is not necessary. There was very wide inter- and to a lesser extent intra-subject variability in pharmacokinetics. Differences in mean values between the routes of administration, even when statistically significant, are small relative to the very wide range of values between subjects.

Safety Evaluation

The test treatments were well tolerated by all subjects with no Serious Adverse Events (SAEs) recorded throughout the study and no subject withdrawals. Peak concentrations of cannabinoids in plasma did not correspond with AEs or other events.

Adverse Events

A summary of treatment-emergent/treatment-related AEs is presented in Table 19. A total of 146 AEs occurred in 12 subjects through-

TABLE 19. Summary of Subjects Who Experienced Treatment Emergent, Treatment Related Adverse Events

Event	*Treatment*			
	A	*B*	*C*	*D*
No. of subjects with ≥ 1 event	12 (100%)	12 (100%)	11 (91.7%)	10 (83.3%)
Cardiac disorders	2	2	1	2
Palpitations	2			
Sinus tachycardia	1	2	1	2
Gastrointestinal disorders	6	6	6	2
Aptyalism				2
Throat irritation	6	6	6	
General disorders and administration site conditions	4	7	6	5
Application site irritation	3	3	4	
Feeling cold		1	1	1
Feeling of relaxation	1	2	1	3
Lethargy	1	1	2	1
Injury, poisoning and procedural complications	2	1	3	2
Drug toxicity NOS	2	1	3	2
Nervous system disorders	9	10	9	9
Coordination abnormal NOS				1
Disturbance in attention	1		1	3
Dizziness	7	5	8	7
Dysgeusia	1	1		
Headache NOS	1	3	1	1
Paraesthesia	2	2		3
Paraesthesia oral NOS	1	3		1
Somnolence	4	3	2	5
Psychiatric disorders	2	2	1	1
Anxiety NEC	1	1		
Dissociation	1	1	1	
Restlessness	1	2	1	1
Skin and subcutaneous tissue disorders	1	0	0	0
Rash maculo-papular	1			

Note: treatment related = definitely, probably, possibly related

out the study. Two events were classified as moderate (flu-like illness and pharyngeal irritation) and the remaining 144 were classified as mild. Three events were classified as not related to test treatment, (flu-like illness, coryza and feels cold), leaving 143 considered to be possibly, probably or definitely related to the test treatment. At the end

of the study, all the events, with the exception of maculo-papular rash of the neck and shoulders, had resolved without treatment. The maculo-papular rash did not require treatment and follow up was continued at the clinical site until resolution.

The most common AEs experienced were dizziness, throat irritation, somnolence, and application site irritation.

The number of subjects experiencing treatment related throat irritation were the same for the sublingual (6), buccal (6) and oro-pharyngeal (6) routes, however there were none reported for the oral capsule. Treatment related application site irritation was experienced with the sublingual (3), buccal (3) and oro-pharyngeal (4), however no application site irritation AEs were reported for the oral capsules. Treatment related paraesthesia was experienced after dosing sublingually (2), buccally (2) and with the oral capsule (3), however no paraesthesia AEs were reported in the subjects receiving PASS oro-pharyngeally.

There were no deaths or SAEs during the study, and no withdrawals due to AEs.

Clinical Laboratory Evaluation

There were no clinically significant changes in the individual or mean haematology or clinical chemistry parameters from pre-dose to post-study (Table 5). There were no haematology or clinical chemistry parameter results (or changes from pre-study to post-study) observed, which were considered to be clinically significant. There were no clinically significant individual subject changes in any safety parameters noted throughout the study. There were no results observed or reported throughout the study that were considered by the investigator to be clinically significant abnormal results.

Vital Signs, Physical Findings and Other Observations Related to Safety

There were no changes in vital signs, physical findings or other safety analyses recorded throughout the study that were considered by the investigator to be clinically significant.

Safety Conclusions

All test treatments were well tolerated by all subjects with no SAEs occurring throughout the study. Most of the AEs experienced by sub-

jects were mild and resolved without treatment. The most common AEs experienced across all test treatments were dizziness, throat irritation, somnolence, and application site irritation. The only notable differences in AEs between test treatment groups were throat irritation and application site irritation, which were not seen with the oral capsule, and paraesthesia which was not seen with oro-pharyngeal dosing.

DISCUSSION AND OVERALL CONCLUSIONS

All routes of administration were well tolerated by all subjects with no SAEs and no withdrawals due to AEs.

There was a wide intra-subject variability in each of the pharmacokinetic parameters. This variation may be due to many factors such as amount of dose swallowed instead of absorption through the oral mucosa, breakfast on the morning of dosing, or levels of exercise undertaken by each subject.

By 720 min (12 h) post-dose mean concentrations of each cannabinoid were still above the LLOQ, indicating that redistribution within the body may still be occurring. The sublingual and oro-pharyngeal routes of administration appear to have the same pharmacokinetic results. The buccal pharmacokinetic parameters are lower when compared to the sublingual and oro-pharyngeal routes. Overall, the results indicate that administration of the liquid spray (GW-1000-02) need not be limited to sublingual administration.

The oral capsule has good bioavailability and provided as is the case here, the formulation is not oil based, may be a viable formulation when self-titration is not necessary. The urine samples were collected in polypropylene containers therefore the reliability of the urine concentration data is not known. Excretion in urine for all four test treatments showed a similar pattern with excretion in significant amounts beginning as the concentrations of THC and 11-hydroxy-THC in plasma were decreasing. This suggests that a portion of the cannabinoids are rapidly metabolised and excreted via the kidneys and are not re-distributed to body tissues such as adipose tissue. In some subjects' excretion of 11-COOH-THC was still occurring pre-next dose suggesting that a portion of the test treatment is re-distributed to body tissues and slowly eliminated via the kidneys. During this slow elimination phase (12 hours to six days), no CBD, THC or 11-hydroxy-THC can be detected in plasma suggesting that after a six day washout period either all THC is metabolised to 11-COOH THC or is re-distributed to other body tissues.

REFERENCES

Agurell, S., M. Halldin, J. E. Lindgren, A. Ohlsson, M. Widman, H. Gillespie, and L. Hollister. 1986. Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man. *Pharmacol Rev* 38 (1):21-43.

British Medical Association. 1997. *Therapeutic uses of cannabis*. Amsterdam: Harwood Academic Publishers.

Baker, P. B., T. A. Gough, and B. J. Taylor. 1983. The physical and chemical features of Cannabis plants grown in the United Kingdom of Great Britain and Northern Ireland from seeds of known origin–Part II: Second generation studies. *Bull Narc* 35 (1):51-62.

GW Pharmaceuticals. 2002. Investigators brochure for cannabis based medicine extract (CBME). Porton Down: GW Pharmaceuticals.

House of Lords. 1998. Cannabis: The scientific and medical evidence. London: House of Lords Select Committee on Science and Technology, Stationery Office.

Maykut, M. O. 1985. Health consequences of acute and chronic marihuana use. *Prog Neuropsychopharmacol Biol Psychiatry* 9 (3):209-38.

McPartland, J. M., and E. B. Russo. 2001. Cannabis and cannabis extracts: Greater than the sum of their parts? *J Cannabis Therapeutics* 1 (3-4):103-132.

Portenoy, R. K. 1990. Chronic opioid therapy in nonmalignant pain. *J Pain Symptom Manage* 5 (1 Suppl):S46-62.

Porter, J., and H. Jick. 1980. Addiction rare in patients treated with narcotics. *N Engl J Med* 302 (2):123.

Whittle, B. A., G. W. Guy, and P. Robson. 2001. Prospects for new cannabis-based prescription medicines. *J Cannabis Therapeutics* 1 (3-4):183-205.