

A Single Centre, Placebo-Controlled,
Four Period, Crossover, Tolerability Study
Assessing, Pharmacodynamic Effects,
Pharmacokinetic Characteristics
and Cognitive Profiles of a Single Dose
of Three Formulations
of Cannabis Based Medicine Extracts
(CBMEs) (GWPD9901),
Plus a Two Period Tolerability Study
Comparing Pharmacodynamic Effects
and Pharmacokinetic Characteristics
of a Single Dose
of a Cannabis Based Medicine Extract
Given via Two Administration Routes
(GWPD9901 EXT)

G. W. Guy
M. E. Flint

G. W. Guy and M. E. Flint are affiliated with GW Pharmaceuticals plc, Porton Down Science Park, Salisbury, Wiltshire, SP4 0JQ, UK.

[Haworth co-indexing entry note]: "A Single Centre, Placebo-Controlled, Four Period, Crossover, Tolerability Study Assessing, Pharmacodynamic Effects, Pharmacokinetic Characteristics and Cognitive Profiles of a Single Dose of Three Formulations of Cannabis Based Medicine Extracts (CBMEs) (GWPD9901), Plus a Two Period Tolerability Study Comparing Pharmacodynamic Effects and Pharmacokinetic Characteristics of a Single Dose of a Cannabis Based Medicine Extract Given via Two Administration Routes (GWPD9901 EXT)." Guy, G. W., and M. E. Flint. Co-published simultaneously in *Journal of Cannabis Therapeutics* (The Haworth Integrative Healing Press, an imprint of The Haworth Press, Inc.) Vol. 3, No. 3, 2003, pp. 35-77; and: *Cannabis: From Pariah to Prescription* (ed: Ethan Russo) The Haworth Integrative Healing Press, an imprint of The Haworth Press, Inc., 2003, pp. 35-77. 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].

<http://www.haworthpress.com/store/product.asp?sku=J175>

© 2003 by The Haworth Press, Inc. All rights reserved.

10.1300/J175v03n03_03

35

SUMMARY. This study was the first study of GW's CBME in man. It was performed in six healthy subjects, employing test treatments consisting of CBD:THC sublingual drops (GW-1011-01): 5 mg Δ^9 -tetrahydrocannabinol (THC) + 5 mg cannabidiol (CBD) per ml of glycerol:ethanol (Eth):propylene glycol (PG) (4:4:2), with peppermint flavouring, High CBD sublingual drops (GW-3009-01): 5 mg CBD per ml of glycerol:Eth:PG (4:4:2), with peppermint flavouring, High THC sublingual drops (GW-2009-01): 5 mg THC per ml of glycerol:Eth:PG (4:4:2), with peppermint flavouring, placebo sublingual drops (GW-4003-01): glycerol:Eth:PG (4:4:2), with peppermint flavouring, aerosol (GW-1009-01): 5 mg CBD + 5 mg THC per ml formulated in propellant:Eth (80:20), and nebuliser (GW-1012-01): 10 mg CBD + 10 mg THC per ml of cremophor (Crem) (0.4):PG (1.5):macrogol (1):dodecanol (0.8):H₂O (7.4), and placebo nebuliser (administered to subjects 005 and 006 instead of the active nebuliser test treatment): Crem (0.4):PG (1.5):macrogol (1):dodecanol (0.8):H₂O (7.4).

Periods 1, 5 and 6 were open label, Periods 2 to 4 double blind. The study was a partially randomised crossover using single doses of THC and/or CBD or placebo. The study drug was administered as sublingual drops according to a pre-determined randomisation scheme in Periods 1 to 4. In Period 5, CBD:THC was administered as a sublingual aerosol and in Period 6 CBD:THC was administered as an inhalation via a nebuliser. There was a six-day washout between each dose.

Primary objectives of the study were to make a preliminary evaluation of the tolerability of cannabis based medicine extracts at single dose in comparison to placebo in order to provide guidance for dosage in future studies; GWPD9901 EXT: was designed to compare the effect of method of administration (sublingually via an aerosol) or the route (inhalation) on the cannabis based medicine extract containing THC and CBD in a ratio of 1:1 in terms of subjective assessment of well-being, *in vivo* pharmacokinetic characteristics over 12 h, the adverse event (AE) profile and measurement of vital signs and conjunctival reddening over 12 h.

Secondary objectives were to compare the effects of the four preparations in terms of cognitive assessment, subjective assessment of well-being *in vivo* pharmacokinetic characteristics over 12 h, the AE profile and measurement of vital signs and conjunctival reddening over 12 h.

The methodology was a six single dose, partially randomised, six-way cross-over study. In Period 1, all subjects received CBD:THC drops. In Periods 2-4, High THC drops, High CBD drops and placebo drops were administered, double blind and fully randomised. In Period 5, all subjects received the aerosol test treatment and in Period 6, all subjects received the nebuliser test treatment.

Each subject received five single doses of a maximum of 20 mg CBD, 20 mg CBD + 20 mg THC and 20 mg THC on five separate occasions

and a placebo dose on one occasion. The duration of the study was six weeks.

Following administration of CBD:THC (Sativex) sublingual drops, mean concentrations of CBD, THC and 11-hydroxy-THC were above the Lower Limit of Quantification (LLOQ) by 45 min post-dose. Plasma concentrations of THC were at least double those of CBD before both decreased below the LLOQ by 360 min and 480 min post-dose, respectively. When High CBD sublingual drops were administered, plasma levels of CBD were generally similar to those measured after CBD:THC sublingual drops. High THC resulted in marginally earlier detection of mean concentrations of both THC and 11-hydroxy-THC and a slightly earlier decline than for CBD:THC sublingual plasma concentrations. Following administration of CBD:THC via the pressurised aerosol, mean quantifiable levels of CBD and THC were detected marginally earlier than for the CBD:THC sublingual drops and declined below the LLOQ marginally later. Plasma concentrations of THC, 11-hydroxy-THC and CBD following administration via the aerosol were lower than after administration of the sublingual drops. Following administration of CBD:THC via the nebuliser, mean plasma levels of both CBD and THC increased rapidly (within 5 min) to levels much higher than measured following administration of the sublingual drops and were maintained until around 120 min post-dose before declining rapidly. Levels of 11-hydroxy-THC were very low compared with those after sublingual dosing.

There were no statistically significant differences in the pharmacokinetics of THC or CBD between CBD:THC sublingual drops and High THC, High CBD or pressurised aerosol. With the exception of a single statistically significant difference in $AUC_{0-\infty}$ for 11-hydroxy-THC following administration of the High THC compared with CBD:THC sublingual drops there were no significant differences in the PK of 11-hydroxy-THC either.

Dosing with the inhaled nebuliser produced marked differences in the pharmacokinetics of CBD and THC compared with CBD:THC sublingual dosing. Peak concentration was greater and much earlier although only C_{max} of CBD and T_{max} of THC were statistically significantly different. Peak concentration and AUCs of 11-hydroxy-THC were statistically significantly less, reflecting reduced early metabolism of THC by this route.

No consistent statistically significant differences were noted between the pharmacokinetic parameters of High CBD, High THC and the aerosol when compared to the CBD:THC sublingual drops. However, the nebuliser resulted in a rapid absorption of CBD and THC and higher peak plasma levels but a reduction in the metabolism of THC to 11-hydroxy-THC.

Subjects experienced a reduction in wakefulness, feeling of well-being, mood, production of saliva and increased hunger and unpleasant effect following administration of each test treatment and placebo. The maximum mean changes in wakefulness, feeling of well-being, mood and production of saliva were reported 3 h post-dose following administration of CBD:THC sublingual drops. Similar trends were also reported following administration of placebo and therefore it is suggested that the effects reported may not be entirely due to active test treatments. The greatest mean incidence of unpleasant effects was reported earlier than for any other effect and following administration of the nebuliser test treatment.

The sublingual test treatments were best liked and the nebuliser test treatment was least liked. All of the subjects (100%) reported coughing and three subjects (50%) reported a sore throat following dosing with the nebuliser.

The sublingual test treatments were well tolerated by all subjects. All six subjects experienced at least two AEs during the study, but there were no deaths, serious adverse events (SAEs) or other significant AEs. The commonest AEs were tachycardia, conjunctival hyperaemia and abnormal dreams.

The small variations in individual subject laboratory parameters and urinalyses and in the mean laboratory parameters did not suggest any patterns or trends. The mean values of all the vital signs showed no patterns or trends either and no differences from placebo. ECGs at both screening and post-study were normal for all subjects.

In conclusion, each sublingual test treatment was well tolerated by all subjects. The inhaled test treatment was not well tolerated and resulted in adverse effects. [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 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 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 (Aguirell 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 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 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 (Portenoy 1990; Porter and Jick 1980). 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.

The CBME GW-1000-02 is 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). The CBME GW-2000-02 is administered as an oromucosal spray, and contains over 90% THC. In this study, the CBME was administered sublingually as drops (GW-1011-01, GW-3009-01, GW-2009-01 and GW-4003-01), a pressurised aerosol (GW-1009-01) and as an inhalation via a nebuliser (GW-1012-01). Each formulation contained either equal amounts of CBD and THC, CBD alone or THC alone.

GWPD9901 was a Phase I clinical study designed to investigate the tolerability, cognitive effects, pharmacokinetic (PK) and pharmacodynamic (PD) effects of CBD and THC when co-administered and administered alone. It was also designed to assess safety and tolerability of the test treatments. It was the first exposure in man of GW's CBME formulations.

STUDY OBJECTIVES

Primary objectives of GWPD9901 were to make a preliminary evaluation of the tolerability of cannabis based medicine extracts (CBMEs) at single dose in comparison to placebo in order to provide guidance for dosage in future studies; while in GWPD9901 EXT: they were to compare the effect of method of administration (sublingually via an aerosol) or the route (inhalation) on the cannabis based medicine extract containing THC and CBD in a ratio of 1:1 in terms of subjective assessment of well-being, *in vivo* pharmacokinetic characteristics over 12 h, the ad-

verse event (AE) profile and measurement of vital signs and conjunctival reddening over 12 h. Secondary objectives of GWPD9901 were to compare the effects of the four preparations in terms of cognitive assessment, subjective assessment of well-being *in vivo* pharmacokinetic characteristics over 12 h, the AE profile and measurement of vital signs and conjunctival reddening over 12 h.

INVESTIGATIONAL PLAN

Periods 1, 5 and 6 were open label, Periods 2 to 4 double blind. The study was a partially randomised crossover using single doses of THC and/or CBD or placebo. In Period 1, each subject received CBD:THC as a series of sublingual drops. In Periods 2 to 4, the High CBD, High THC and placebo were administered as a series of sublingual drops according to a pre-determined randomisation scheme. In Period 5, the aerosol test treatment was administered sublingually via a pressurised aerosol and in Period 6 the test treatment was administered as an inhaled dose via a nebuliser. There was a minimum washout period of six-days between each dose.

Blood samples were taken for plasma concentration analysis and blood pressure (BP) and pulse, cognitive testing (Periods 1 to 4 only) and PD effects were measured and recorded at pre-determined times during each study period.

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

The CBD:THC sublingual drops were administered in Period 1 as the combination of CBD and THC was thought to be safest and allow assessment of the tolerability of the other test treatments. High CBD, High THC and placebo sublingual drops were then fully randomised to prevent period effect and this part of the study was also double blind to ensure no bias was introduced when recording AEs and other parameters.

The pressurised aerosol and inhaled nebuliser routes of administration were chosen to assess different methods of dose administration. These doses were not blinded or randomised due to the contrasting method of administration.

Subjects were admitted to the clinical unit the evening before dosing (Day - 1) to allow dietary control and eligibility assessments to be made. Dose administration was in the morning of Day 1 of each period to al-

low for measurements/assessments to be carried out up to 12 h post-dose with minimal disruption to the subjects sleep. A crossover design was chosen to enable both inter- and intra-subject comparisons of the data collated. A six-day washout period was chosen as it was estimated that plasma concentrations of cannabinoids would be below the Lower Limit of Quantification (LLOQ) before administration of the next dose and to facilitate scheduling within the clinical unit.

This was a proof of concept study and therefore a small number of subjects (six) were required.

INCLUSION CRITERIA

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

1. Were aged 30-45 years.
2. Weighed between 50-90 kg inclusive and body mass index (BMI) no greater than 30 kg/m².
3. Were willing and able to undertake all study requirements including pre- and post-study medical screening.
4. Had given written informed consent.
5. Female: were surgically sterilised or were taking adequate contraceptive precautions.
6. Male: agreed to use barrier methods of contraception both during and for three months after completing the study.
7. Were cannabis experienced but had abstained for a minimum of 30 days prior to receiving the first dose.

EXCLUSION CRITERIA

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

1. Had evidence of clinically significant cardiovascular, haematological, hepatic, gastro-intestinal, renal, pulmonary, neurological or psychiatric disease.
2. Had a history of schizophrenic-type illness.
3. Had a history of chronic alcohol or drug abuse or any history of social drug abuse other than experience with cannabis.

4. Had a resting systolic blood pressure (SBP) greater than 140 mmHg or diastolic blood pressure (DBP) greater than 90 mmHg.
5. Had a history of sensitivity to cannabis or multiple allergies or drug sensitivities.
6. Had a history of asthma.
7. Were currently taking any medication including self-medication.
8. Had taken a regular course of medication within the four weeks prior to first test treatment administration.
9. Had taken any medication within the fourteen days prior to first test treatment administration except for vitamins (which were required to be discontinued at screening), or the occasional use of paracetamol or, for females only, contraceptive preparations.
10. Had been hospitalised for any reason within the twelve weeks prior to first test treatment administration.
11. Had lost or donated greater than 400 ml of blood in the twelve weeks prior to first test treatment administration.
12. Had participated in a clinical trial in the 12 weeks prior to first test treatment administration.
13. Smoked more than five cigarettes a day.
14. Consumed more than 21 units of alcohol per week (male) or 14 units (female).
15. Had positive results for Hepatitis B or C, or Human Immunodeficiency Virus (HIV) 1 or 2 screening.
16. Had clinically significant biochemistry, haematology or urinalysis results at screening.
17. Were pregnant or lactating (females).
18. Refused to use the designated contraceptive precautions (male or female).
19. Failed to pass the Hospital Depression and Anxiety Scale (HADS) (reference to the Cognitive Assessment tests).
20. Were found to be colour blind (Ishihara colour blind screening).

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 48h pre-each dose until the end of each confinement period;

- ii. Drinking more than 3 units (male) or 2 units (female) of alcohol per day during non-restricted days.
- iii. Taking any drugs, including drugs of abuse, prescribed and/or over-the-counter medications for four weeks prior to first dose and for the duration 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.

TEST TREATMENTS ADMINISTERED

All subjects received a single dose of the allocated test treatment on Day 1 of each of the six periods. All subjects received five single doses (maximum of 20 mg CBD and/or THC per dose) of CBD and/or THC and one placebo dose. Preparations were as follows (Table 1).

Test treatments consisted of CBD:THC sublingual drops (GW-1011-01): 5 mg Δ^9 -tetrahydrocannabinol (THC) + 5 mg cannabidiol (CBD) per ml of glycerol:ethanol (Eth):propylene glycol (PG) (4:4:2), with peppermint flavouring, High CBD sublingual drops (GW-3009-01): 5 mg CBD per ml of glycerol:Eth:PG (4:4:2), with peppermint flavouring, High THC sublingual drops (GW-2009-01): 5 mg THC per ml of glycerol:Eth:PG (4:4:2), with peppermint flavouring.

TABLE 1. Product Codes, Batch Numbers and Expiry Dates for Each Test Treatment

<i>Treatment</i>	<i>Batch No.</i>	<i>Product Code</i>	<i>Expiry Date</i>	<i>Total Dose</i>	<i>No. of Drops/Sprays/ Inhalations</i>
CBD:THC SL Drops	90903	GW-1011-01	Oct 31, 1999	20 mg CBD + 20 mg THC	8 (10 mins apart)
CBD SL Drops	90902	GW-3009-01	Oct 31, 1999	20 mg CBD	8 (10 mins apart)
THC SL Drops	90901	GW-2009-01	Oct 31, 1999	20 mg THC	8 (10 mins apart)
Aerosol	91001	GW-1009-01	Nov 21, 1999	20 mg CBD + 20 mg THC	8 (10 mins apart)
Nebuliser	91002	GW-1012-01	Oct 27, 1999	20 mg CBD + 20 mg THC	series of 50 breaths (5 mins apart)

SL = sublingual

erol:Eth:PG (4:4:2), with peppermint flavouring, placebo sublingual drops (GW-4003-01): glycerol:Eth:PG (4:4:2), with peppermint flavouring, aerosol (GW-1009-01): 5 mg CBD + 5 mg THC per ml formulated in propellant:Eth (80:20), and nebuliser (GW-1012-01): 10 mg CBD + 10 mg THC per ml of cremophor (Crem) (0.4):PG (1.5):macrogol (1):dodecanol (0.8):H₂O (7.4), and placebo nebuliser (administered to subjects 005 and 006 instead of the active nebuliser test treatment): Crem (0.4):PG (1.5):macrogol (1):dodecanol (0.8):H₂O (7.4).

Each test treatment container was identified with no less than study number, subject number, period number, unit number and expiry date. All subjects received CBD:THC sublingual drops in Period 1, the aerosol test treatment in Period 5 and the inhaled nebuliser test treatment in Period 6. High CBD, High THC and placebo sublingual drops were randomised in Periods 2 to 4 according to the randomisation scheme. The doses were chosen as they were considered to be the average dose of cannabinoids received by smoking a cannabis cigarette. Subjects were allowed to stop dosing at any time if effects were too unpleasant. The Principal Investigator was also permitted to stop dosing before the maximum of 20 mg CBD and/or 20 mg THC was achieved if it was considered that the PD effects were too great.

Subjects 005 and 006 received placebo via the nebuliser to determine if the adverse effects that subjects 001 to 004 had experienced were due to the method of administration or the active ingredient.

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 for measurements to be taken and procedures to be carried out to prevent the subjects being confined to the clinical unit overnight after dosing. A minimum of six-days washout between each dose was specified as it was considered that by that time, plasma cannabinoid concentrations would be below the LLOQ.

BLINDING

Periods 1, 5 and 6 were open label. Periods 2 to 4 were double blind. Unblinding envelopes were retained at the study centre and a duplicate set was retained at GW. All subjects completed the study without any serious adverse events (SAEs), therefore unblinding of any subject test treatment was not required. Upon completion of the in-life phase of the study, all unblinding envelopes were returned to GW intact.

Subjects were required to abstain from taking any medication in the 14 days, and/or taking a course of medication in the four weeks prior to the study commencing. Any medications taken by subjects during the study (screening to post-study examination) were recorded in the Case Report Form (CRF) and Investigator judgement as to the subjects' continued eligibility was made.

TREATMENT COMPLIANCE

Subjects were dosed by the Principal Investigator or suitably trained designee. For the sublingual drops and pressurised aerosol test treatments, subjects were instructed to allow each drop/spray to absorb under their tongue and not to swallow for as long as possible. For the nebuliser test treatment, subjects were instructed to breathe normally whilst inhaling through the nebuliser. The nebuliser was breath activated and subjects were instructed to inhale for 50 breaths over approximately 5 min, stop and repeat after 10 min. This process was required to be repeated until the maximum dose was reached or dosing was stopped. The actual time of administration of each drop/spray was recorded in the CRF and the dosing procedure was witnessed by a dose verifier. Due to a problem with the nebuliser, which did not give the required dose over 50 breaths, subjects were permitted to take more than 50 breaths per series.

PRE-STUDY SCREENING

Subjects were required to undergo a pre-study screen no more than 14 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.

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.

Concomitant Medications and Medical History

Subjects were asked to provide details of any drugs, vitamins or medications they had taken in the previous four weeks or were currently taking. If taking vitamins or paracetamol at screening, subjects were required to stop taking them at screening to be eligible for the study. Previous medical history details were also recorded.

Physical Examination

Subjects underwent a physical examination to determine if there are any abnormalities in any body systems. Blood pressure (systolic/diastolic) and pulse were measured after the subject had been seated for no less than 5 min. A 12-lead electrocardiogram (ECG) was taken for each subject and assessed using the usual parameters.

Microscopy was required to be carried out on any abnormal urine samples. A pregnancy test was carried out on all urine samples from female subjects. The samples provided (male and female) were also used to screen for drugs of abuse. A blood sample was taken in an EDTA blood tube for haematology. A blood sample was taken in a gel blood tube for clinical chemistry. A blood sample was taken in a gel blood tube to screen for the presence of Hepatitis B and/or C and/or HIV.

Subjects were required to complete the HADS test and the Ishihara Colour Blindness test.

PRE-DOSE PROCEDURES

The day before dosing for Period 1, subjects were required to attend the clinical unit in the afternoon to complete a baseline well-being questionnaire and cognitive assessment. In all other periods, subjects were required to arrive at the clinic at approximately 11 h prior to dosing (i.e., the previous evening). A snack was provided at approximately 21:00 and thereafter subjects were required to fast until 4 h post-dose. Subjects were required to complete the Adult Reading Test. On the morning of each dosing day, each subject's health status was updated and pre-dose procedures (blood pressure and pulse, alcohol and drug of abuse screen and pregnancy test for female subjects) were carried out.

Within the 30 min before dosing started the following pre-dose procedures were carried out: cardiac monitoring was started, blood pressure and pulse recorded, conjunctival reddening assessed and a well-being questionnaire completed. The pre-dose blood sample was also taken.

Blood Sampling for Plasma Concentration Analysis

Blood samples (5 ml) were collected into 5 ml lithium heparin blood tubes via indwelling cannula or individual venipuncture. Samples were placed immediately into an ice bath until centrifuged (1000 G for 10 min at 4°C). The resultant plasma was decanted into two identical pre-labelled amber glass plasma tubes and placed in a freezer at -20°C.

Blood samples were collected pre-dose and at 5, 10, 15, 30 and 45 min and at 1, 2, 3, 4, 6, 8 and 12 h post-dose.

Plasma Concentration Analytical Procedures

Plasma concentrations of CBD, THC and 11-hydroxy-THC were measured in each plasma sample according to the analytical protocol.

SAFETY ASSESSMENTS

Urine Drug Screen

Urine drug screens were required to be carried out at check-in for each study period. The drug screen was required to be negative for all drugs pre-dose Period 1. In subsequent periods, 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.

Blood Pressure and Pulse

Subjects' blood pressure and pulse were measured pre-dose then at 5, 10, 15, 30 and 45 min and at 1, 2, 3, 4, 6, 8 and 12 h post-dose.

Cardiac Monitoring

Cardiac monitoring was carried out continually from pre-dose to 4 h post-dose for each subject. A print out from the monitor was retained with the study centre study files.

Conjunctival Redness

Subjects were visually assessed for conjunctival reddening at the following times: pre-dose, 15, 30 and 45 min and at 1, 2, 4, 8 and 12 h post-dose. The extent of reddening was scored according to Table 2.

TABLE 2. Conjunctival Reddening Guidelines

<i>Condition</i>	<i>Score</i>
No reddening apparent	0
Slight reddening	1
Moderate reddening	2
Severe reddening	3

Adverse Events

Subjects' health was monitored continuously throughout the study. Subjects were also encouraged to inform the clinical staff of any changes in their health as soon as possible. All AEs were recorded in the CRF and followed to resolution or at the discretion of the Investigator.

Cognitive Assessments

Cognitive tests were carried out in Periods 1 to 4 only, using the Cambridge Neuropsychological Test Automated Battery (CANTAB), supplied by CeNeS, Histon, Cambridgeshire, UK. Subjects were asked to complete cognitive tests on the day before dose in Period 1 (baseline), and in each period at 10 min post last actuation then at 3 and 8 h post-dose.

Well-Being Questionnaire

Subjects were required to complete a series of visual analogue scales for alertness, well-being, mood, dryness of mouth, hunger level and any unpleasant effects. These were carried out on Day - 1 and then in each period pre-dose, 10 min and 3, 8 and 12 h post-dose.

FOOD AND BEVERAGES

Dietary Restrictions

The subjects were instructed not to consume alcohol or caffeine-containing food or drink from 48 h before dosing in each period until after they were discharged from the clinical unit. During treatment free days

subjects were required to limit their alcohol intake to no more than three units per day (males) or two units per day (females).

A snack was provided at 21:00 on the evening before dosing, thereafter subjects were required to fast until 4 h post-dose. After 4 h post-dose, decaffeinated drinks were provided *ad libitum*. Lunch and dinner were provided at 4 and 9 h post-dose, respectively. Subjects were provided with breakfast prior to discharge at 24 h post-dose. With the exception of the snack at 13 h post-dose and breakfast on Day 2, subjects were required to eat the entire meals provided. The details of diet are presented in Table 3.

Check-Out Procedures

Following breakfast on Day 2 (approximately 24 h post-dose) of each study period and if deemed well enough to leave by the Investigator, subjects were discharged from the clinical unit. Prior to discharge, any ongoing AEs were updated and follow-up arranged if required.

Post-Study Screening

Each subject was required to return to the clinical unit no more than ten days post last dose to undergo a post-study examination. This consisted of a physical examination, blood samples taken for haematology and clinical chemistry, urinalysis, a 12-lead ECG and vital signs recorded. Any ongoing AEs were updated and, if required, arrangements were made to follow up with the subjects.

TABLE 3. Suggested Menu

<i>Meal</i>	<i>Time</i>	<i>Content</i>
Evening Meal	Day -1, 21:00	Two filled rolls One light desert (e.g., yoghurt) One piece of fruit Decaffeinated drink
Lunch	Day 1, 4 h post-dose	Cooked meal (e.g., meat and two vegetables) Dessert
Evening Snack	Day 1, 13 h post-dose	Optional, no restrictions
Breakfast	Day 2	Optional, no restrictions

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 GCP, internal Standard Operating Procedures (SOPs), working practices and protocol requirements. Monitoring of the study progress and conduct was carried out by the Clinical Department of GW according to GW SOPs and was ongoing throughout the study.

Standardisation of Laboratory Procedures

Analysis of safety bloods (haematology and clinical chemistry) was carried out by Unilabs UK (previously J S Pathology Ltd).

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 the CRF.

Clinical Data Management

Data were double entered into approved data tables using Microsoft Excel software. Manual checks for missing data and inconsistencies were carried out and queries were raised for any resulting issues.

Once the data were clean, i.e., no outstanding queries, then Quality Control (QC) checks of 100% of the data for a 10% sample of the patients were conducted to make a decision on the acceptability of the data. Any errors were resolved and any error trends across all subjects were also corrected. Upon completion of the QC step, the data sets were burnt onto a compact disc.

Quality Assurance Audits

Clinical Quality Audits were carried out.

Statistical and Analytical Plans

The statistical analysis was carried out as indicated in the protocol. All statistical analyses were performed using SAS® for Windows (v8) software.

Pharmacokinetic Analysis

All p-values quoted are two-sided. No blood samples were missed in the subjects who were dosed therefore all subjects were deemed evaluable for and were included in pharmacokinetic analyses. The pharmacokinetic parameters calculated were as noted in Table 4.

Summary statistics were calculated for each pharmacokinetic parameter and treatment (arithmetic mean, number (N), standard deviation (SD), coefficient of variance (CV%), minimum and maximum for all parameters and additionally the geometric mean for AUC_{0-t} , $AUC_{0-\infty}$ and C_{max}). AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} were natural log transformed prior to analysis and T_{max} was analysed untransformed; $t_{1/2}$ and K_{el} were summarised only. Each parameter was analysed using analysis of variance (ANOVA) with subject and treatment as factors. Least square (LS) means were presented for each test treatment. Point estimates (differences between least square means) for the contrasts between each of High THC, aerosol and inhaler with CBD:THC were presented with the corresponding 95% confidence intervals (CI); for the log-transformed variables, the contrasts were first back transformed to provide ratios and corresponding 95% confidence intervals. The distribution of T_{max} was also summarised.

TABLE 4. Pharmacokinetic Definitions

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 ≤ 12h) 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}	The elimination rate constant.

Pharmacodynamic Analysis

All subjects who completed at least one study period were evaluable for pharmacodynamic analysis. All pharmacodynamic parameters were summarised by test treatment group and analyte. Data for conjunctival reddening and well-being questionnaire were summarised descriptively by time point and treatment (arithmetic means, N, SDs, medians, minima and maxima or counts and percentages, as appropriate). The changes from pre-dosing for the well-being questionnaire were summarised similarly. Analysis of the cognitive assessments was carried out by CeNeS Ltd.

SAFETY ANALYSIS

Adverse Events

All AEs were coded by Medical Dictionary of Regulatory Activities (MedDRA) and presented by system organ class (SOC) and preferred term (PT). Laboratory data collected pre and post-study were summarised descriptively (N, mean, SD, median, minimum and maximum) at each of the two time-points and also as the change from pre-study to post-study.

Blood Pressure and Pulse

For 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 in means from pre-dose. Blood pressure and pulse data are listed for each subject at each time point.

12-Lead ECG

For each of the ECG parameters (heart rate (HR), PR interval, QT interval and QRS width), descriptive statistics (N, mean, SD, median, minimum and maximum) were calculated and summarised pre- and post-study.

Determination of Sample Size

No formal sample size calculation was carried out for this study, as it was a "First in man" safety and tolerability study.

Changes in the Conduct of the Study or Planned Analyses

The protocol stated that the pharmacokinetic parameters AUC_{0-t} , C_{max} , C_{res} and T_{max} would be evaluated. In accordance with standard practice, T_{max} , C_{max} , AUC_{0-t} , $AUC_{0-\infty}$ were evaluated and compared between treatments. In addition, $t_{1/2}$ and K_{el} were summarised only.

Study Subjects

Three healthy male and three healthy female subjects were required to complete the study in its entirety. 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. Only one minor protocol deviation was reported throughout the study. One subject consumed caffeine in the 48 h prior to dosing for Period 4. This was not considered by the Investigator to affect the subject's eligibility and is not considered to affect the integrity of the study.

Plasma Concentration and Pharmacokinetic Evaluation

Six healthy subjects (three male and three female) were required to complete the study in its entirety. Six subjects (001 to 006) who were randomised in the study were included in the data analysis.

Demographic and Baseline Characteristics

All subjects included in the study complied with all demographic and baseline requirements.

Measurements of Compliance

Each test treatment was administered by suitably trained clinical staff. No deviations to the dosing regimen were noted for any subject throughout the study.

INDIVIDUAL PLASMA CONCENTRATION DATA AND PHARMACOKINETIC RESULTS

Analysis of Plasma Concentration Results

Plasma samples were analysed for CBD, THC and 11-hydroxy-THC according to the analytical protocol. Analytical results were produced

in tabular form and concentration-time graphs were produced from these data. Mean plasma concentrations are summarised in Table 5.

The LLOQ was 1 ng/ml. Data below the LLOQ are presented as <1 and the actual value measured is presented in parenthesis. The actual values measured were used when creating graphs.

CBD:THC Sublingual Drops

Mean concentrations of CBD, THC and 11-hydroxy-THC were above the LLOQ by 45 min post-dose (Figure 1) (range of individual times: 45-180 min, CBD; 30-120 min THC and 11-hydroxy-THC). Mean concentrations of THC (Table 6) were at least double those of CBD throughout the sampling period and from 120 min to the end of sampling mean concentrations of 11-hydroxy-THC were approximately double those of THC (CBD 1.23 ng/ml, THC 3.13 ng/ml, 11-hydroxy-THC 6.68 ng/ml). By 360 and 480 min post-dose the mean level of CBD and THC, respectively and all individual levels were below the LLOQ.

High CBD Sublingual Drops

Mean concentrations of CBD were above the LLOQ by 30 min post-dose (range: 30-120 min), peaked at 120 min (1.49 ng/ml) and

TABLE 5. Mean Plasma Concentration Data

Time (min)	Mean Plasma Concentrations											
	CBD				THC				11-Hydroxy THC			
	CBD: THC SL Drops	High CBD SL Drops	Aerosol	Nebuliser	CBD: THC SL Drops	High THC SL Drops	Aerosol	Nebuliser	CBD: THC SL Drops	High THC SL Drops	Aerosol	Nebuliser
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	0.00	0.00	0.00	6.81	0.00	0.00	0.00	9.45	0.00	0.00	0.00	0.00
10	0.00	0.00	0.00	3.26	0.00	0.00	0.00	5.88	0.00	0.00	0.00	0.26
15	0.00	0.00	0.24	5.04	0.00	0.21	0.23	6.50	0.00	0.00	0.00	0.22
30	0.00	0.33	0.48	5.40	0.19	1.03	1.00	8.25	0.34	1.17	0.72	0.43
45	0.60	0.58	0.96	2.91	1.64	1.71	1.49	4.44	1.70	2.57	1.68	0.24
60	1.20	0.93	0.97	4.56	3.04	3.33	1.87	6.74	3.51	4.36	2.56	0.55
120	1.64	1.49	0.73	0.96	4.67	3.86	2.38	2.31	7.43	5.19	4.84	0.29
180	1.23	0.73	0.86	0.39	3.13	2.94	2.36	0.91	6.68	4.81	5.07	0.20
240	0.48	0.45	0.60	0.29	1.70	1.34	1.38	0.36	4.82	3.14	3.90	0.00
360	0.00	0.00	0.99	0.00	0.55	0.00	1.30	0.00	2.43	1.01	2.89	0.00
480	0.00	0.00	0.22	0.00	0.00	0.00	0.22	0.00	1.05	0.23	1.40	0.00
720	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.20	0.00	0.17	0.00

FIGURE 1. GWPD9901: Mean Plasma Cannabinoid Concentrations Following Administration of CBD:THC, 1:1 Sublingual Drops

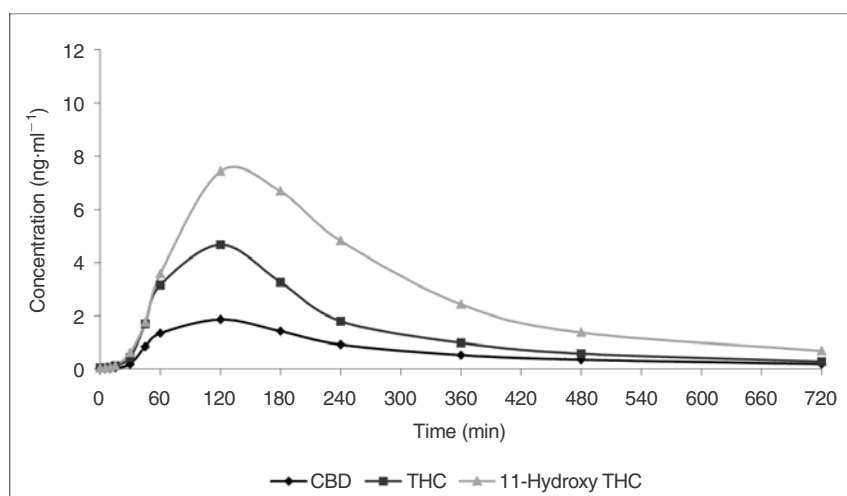


TABLE 6. Mean Pharmacokinetic Parameters

Time (min)	Mean Pharmacokinetic Parameters				
	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (ng/ml.min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (ng/ml.min)
CBD					
CBD:THC SL Drops	100	2.58	209.30	118.33	578.89
High CBD SL Drops	130	2.05	156.13	NC	NC
Aerosol	141	2.60	325.93	143.77	811.75
Nebuliser	36	9.49	564.35	65.71	726.81
THC					
CBD:THC SL Drops	100	6.50	737.48	78.53	928.42
High THC SL Drops	110	5.77	628.80	65.53	818.10
Aerosol	130	3.69	636.11	83.00	776.09
Nebuliser	32	12.46	786.33	47.13	899.77
11-Hydroxy THC					
CBD:THC SL Drops	140	8.25	1842.75	117.68	2066.30
High THC SL Drops	110	7.29	1163.78	99.55	1373.19
Aerosol	160	6.23	1568.20	138.11	1838.04
Nebuliser	38	1.65	65.15	132.56	495.67

NC = Not acceptable

thereafter declined such that they were below the LLOQ by 360 min in all subjects (Figure 2). Mean plasma concentrations of CBD were generally similar to those seen for CBD:THC sublingual drops (Table 6). Neither THC nor 11-hydroxy-THC was detected in quantifiable amounts throughout the sampling period.

High THC Sublingual Drops

Mean concentrations of THC were above the LLOQ by 15 min post-dose (individual range: 15-60 min) (Figure 3), which was marginally earlier than for the CBD:THC sublingual drops (45 min post-dose). Mean concentration reached a peak around 120 min (3.86 ng/ml) (Table 6) and by 360 min had declined below the LLOQ. Mean concentrations of 11-hydroxy-THC were above the LLOQ by 30 min post-dose (individual range: 30-60 min) (Figure 3), which was also marginally earlier than for the CBD:THC sublingual drops (45 min post-dose). Mean concentration reached a peak around 120 min (5.19 ng/ml) and by 480 min had declined below the LLOQ. Concentrations of THC and 11-hydroxy-THC were generally similar to those seen after the CBD:THC sublingual drops.

FIGURE 2. GWPD9901: Mean Plasma Cannabinoid Concentrations Following Administration of High CBD Sublingual Drops

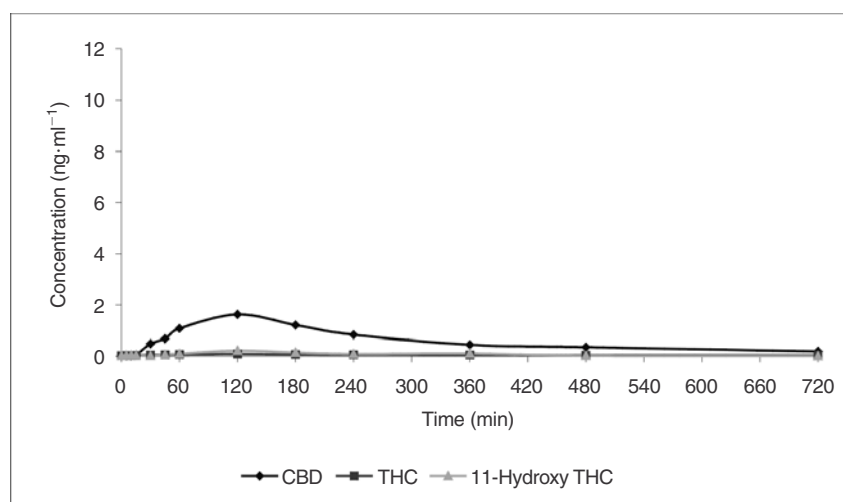
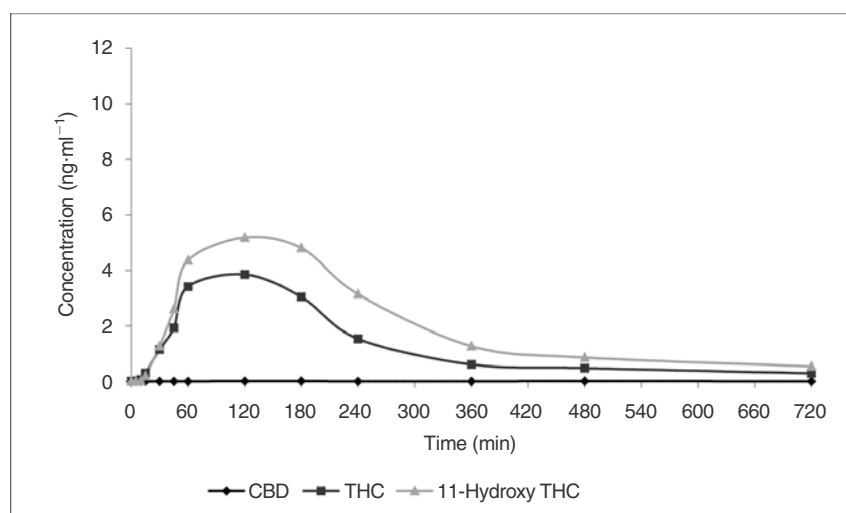


FIGURE 3. GWPD9901: Mean Plasma Cannabinoid Concentrations Following Administration of High THC Sublingual Drops



Placebo Sublingual Drops

Following placebo dosing no quantifiable amount of any cannabinoid was detected in any subject during the sampling period.

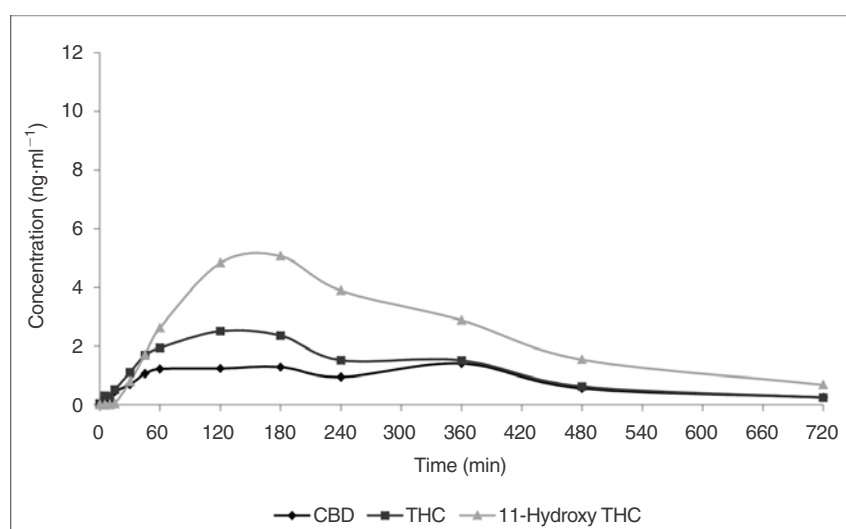
Pressurised Aerosol

Mean concentrations of CBD and THC above the LLOQ were detected in plasma by 15 min post-dose (range 10-180 min for CBD (excepting Subject 006 for whom concentrations remained below LLOQ); 15-180 min for THC) which was marginally earlier than for the CBD:THC sublingual drops (Figure 4).

Mean concentrations of CBD show two similar peak levels at 60 and 360 min (0.97 and 0.99 ng/ml, respectively) (Figure 4) reflecting the variability in the time of peak plasma concentration (range 45-360 min) between individuals. Mean concentrations of CBD had declined below LLOQ by 720 min.

Mean concentrations of THC peaked around 120-180 min (2.38 ng/ml, 2.36 ng/ml) and had declined below LLOQ by 720 min (Figure 4). Mean concentrations of 11-hydroxy-THC above the LLOQ were de-

FIGURE 4. GWPD9901 Extension: Mean Plasma Cannabinoid Concentrations Following Administration of CBD:THC 1:1 Aerosol



tected in plasma by 30 min post-dose (range: 30-120 min), peaked around 180 min (5.07 ng/ml) and then declined more slowly than THC or CBD and remained above the LLOQ at 720 min (Figure 4).

Mean concentrations of THC were generally greater than those for CBD but less than mean concentrations of 11-hydroxy-THC (Table 6). Mean concentrations of CBD, THC and 11-hydroxy-THC following the pressurised aerosol were generally higher than for the CBD:THC sublingual drops from 45-60 min to 240 min and were lower than for the CBD:THC sublingual drops at almost all other time points. At 360 min to 720 min post-dose mean concentrations of each cannabinoid were marginally greater for the pressurised aerosol than for the CBD:THC sublingual drops.

Following administration of the test treatment via the pressurised aerosol, mean concentrations of each cannabinoid in plasma were above the LLOQ for longer when compared to the CBD:THC sublingual drops.

Inhaled Nebuliser

The dose administered via the inhaled nebuliser was approximately half that of the sublingual drops and aerosol. Mean concentrations of

CBD and THC were above the LLOQ by 5 min post-dose (range 5-30 min for both CBD and THC) and each cannabinoid was detected in plasma notably earlier than the CBD:THC sublingual drops (Figure 5).

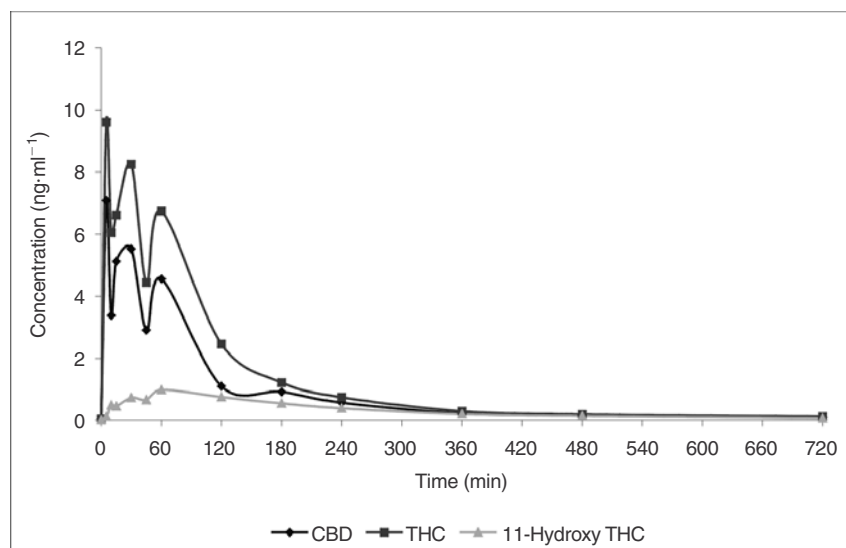
Mean concentrations of CBD fluctuated considerably between 5 min and 60 min post-dose, reflecting the variability in levels and timing of peak concentrations in individuals, but were considerably higher than following the other treatments.

Mean concentrations of THC were higher than corresponding concentrations of CBD and also fluctuated considerably between 5 min and 60 min post-dose, reflecting the individual variability.

Mean concentrations of both CBD and THC declined rapidly from 60 min. CBD concentrations were below the LLOQ in all but one subject at 180 min and THC in all but one subject by 240 min.

Mean concentrations of 11-hydroxy-THC were much lower than corresponding concentrations of both CBD and THC and much less than following the other treatments (Figure 5). In three subjects, levels of 11-hydroxy-THC failed to rise above the LLOQ at all during the sampling period.

FIGURE 5. GWPD9901 Extension: Mean Plasma Cannabinoid Concentrations Following Administration of CBD:THC, 1:1 Nebuliser



Analysis of Pharmacokinetic Parameters

PK parameters were calculated using WinNonlin® Professional 3.1. The model used was a non-compartmental, linear trapezoidal analysis. Values below the LLOQ were not used when calculating PK parameters. Mean values are presented in (Table 6).

The PK parameters for each test treatment (with the exception of placebo) were statistically compared to the PK parameters for the CBD:THC sublingual drops. Due to the low concentrations of cannabinoids in plasma some individual PK parameters were not calculable and therefore some of the mean PK parameters are not based on all six subjects.

CBD:THC Sublingual Drops

Following the CBD:THC sublingual drops arithmetic mean T_{max} of CBD (Table 7) and THC (Table 8) was 100 and 100 min, respectively. Arithmetic mean C_{max} of CBD was 2.58 ng/ml, arithmetic mean AUC_{0-t} 209.3 ng/ml.min and $AUC_{0-\infty}$ 578.89 ng/ml.min. The corresponding values for THC were greater as C_{max} was 6.50 ng/ml, AUC_{0-t} 737.48 ng/ml.min and $AUC_{0-\infty}$ 928.42 ng/ml.min. The arithmetic mean T_{max} of 11-hydroxy-THC was 140 min (Table 9). Arithmetic mean C_{max} was 8.25 ng/ml, arithmetic mean AUC_{0-t} 1842.75 ng/ml.min and $AUC_{0-\infty}$ 2066.30 ng/ml.min.

High CBD Sublingual Drops

The mean PK parameters for CBD following administration of High CBD sublingual drops were not statistically significantly different from

TABLE 7. CBD Pharmacokinetic Parameters: CBD:THC Sublingual Drops

Subject	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (min*ng/ml)	K_{el} (1/min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (min*ng/ml)
1	120	3.70	264.00	NC	NC	NC
2	60	2.63	449.18	0.0048	144.57	749.51
3	60	1.95	14.63	NC	NC	NC
4	180	2.75	208.50	NC	NC	NC
5	60	2.64	266.10	0.0075	92.10	408.27
6	120	1.78	53.40	NC	NC	NC
Mean	100	2.58	209.30	0.0062	118.33	578.89
SD**	60-180	0.68	158.72	0.0019	37.10	241.29

** T_{max} presented as minimum-maximum
NC = Not calculable

TABLE 8. THC Pharmacokinetic Parameters: CBD:THC Sublingual Drops

Subject	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (min*ng/ml)	K_{el} (1/min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (min*ng/ml)
1	120	9.29	880.28	0.0157	44.28	971.00
2	60	6.44	1005.75	0.0076	90.62	1327.35
3	60	5.62	287.85	0.0218	31.80	357.60
4	180	6.31	916.20	0.0077	89.71	1118.09
5	60	4.93	549.98	0.0083	83.77	686.54
6	120	6.38	784.80	0.0053	131.02	1109.93
Mean	100	6.50	737.48	0.0111	78.53	928.42
SD**	60-180	1.49	269.76	0.0063	35.81	350.49

** T_{max} presented as minimum-maximum
NC = Not calculable

TABLE 9. 11-Hydroxy THC Pharmacokinetic Parameters: CBD:THC Sublingual Drops

Subject	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (min*ng/ml)	K_{el} (1/min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (min*ng/ml)
1	120	12.14	2459.40	0.0089	78.21	2586.89
2	180	7.87	1996.05	0.0060	115.20	2205.45
3	60	6.52	1208.85	0.0075	92.51	1343.65
4	240	7.22	2371.80	0.0045	153.34	2635.06
5	120	6.95	1459.20	0.0057	122.16	1758.81
6	120	8.82	1561.20	0.0048	144.64	1867.94
Mean	140	8.25	1842.75	0.0062	117.68	2066.30
SD**	60-240	2.07	512.22	0.0017	29.04	503.98

** T_{max} presented as minimum-maximum
NC = Not calculable

the CBD:THC sublingual drops (Table 10). The arithmetic mean T_{max} was 130 min and arithmetic mean C_{max} 2.05 ng/ml, arithmetic mean AUC_{0-t} was numerically lower than following the CBD:THC sublingual drops at 156.13 ng/ml.min. $AUC_{0-\infty}$ was not calculable as there were generally few time points in any subjects when plasma levels of CBD exceeded the LLOQ (at a single sampling time in three subjects).

High THC Sublingual Drops

Only mean $AUC_{0-\infty}$ for 11-hydroxy-THC following administration of the High THC sublingual drops (Table 11) was statistically signifi-

TABLE 10. CBD Pharmacokinetic Parameters: High CBD Sublingual Drops

Subject	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (min*ng/ml)	K_{el} (1/min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (min*ng/ml)
1	240	1.32	185.40	NC	NC	NC
2	120	3.17	563.03	0.0135	51.18	664.93
3	120	1.90	57.00	NC	NC	NC
4	60	3.21	49.73	NC	NC	NC
5	120	1.14	34.20	NC	NC	NC
6	120	1.58	47.40	NC	NC	NC
Mean	130	2.05	156.13	NC	NC	NC
SD**	60-240	0.92	207.01	NC	NC	NC

** T_{max} presented as minimum-maximum
NC = Not calculable

TABLE 11. 11-Hydroxy THC Pharmacokinetic Parameters: High THC Sublingual Drops

Subject	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (min*ng/ml)	K_{el} (1/min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (min*ng/ml)
1	120	6.74	1105.05	0.0070	98.38	1261.17
2	120	7.97	1793.18	0.0072	96.32	1983.56
3	60	6.21	669.83	0.0055	126.84	944.30
4	180	7.83	1292.70	0.0091	76.32	1456.75
5	120	6.67	1205.63	0.0065	105.95	1441.02
6	60	8.31	916.28	0.0074	93.49	1152.32
Mean	110	7.29	1163.78	0.0071	99.55	1373.19
SD**	60-180	0.85	380.32	0.0012	16.58	354.80

** T_{max} presented as minimum-maximum
NC = Not calculable

cantly lower when compared to the CBD:THC sublingual drops (1373.19 ng/ml.min vs. 2066.30 ng/ml.min, $p = 0.0358$). For THC (Table 12), T_{max} was 110 min, C_{max} 5.77 ng/ml, AUC_{0-t} 628.80 ng/ml and $AUC_{0-\infty}$ 818.10 ng/ml. C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were slightly lower than following the CBD:THC sublingual drops and T_{max} was slightly later but these differences were not statistically significant.

Pressurised Aerosol

There were no statistically significant differences in PK parameters for CBD (Table 13), THC (Table 14) or 11-hydroxy-THC (Table 15)

TABLE 12. THC Pharmacokinetic Parameters: High THC Sublingual Drops

Subject	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (min*ng/ml)	K_{el} (1/min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (min*ng/ml)
1	120	5.46	708.45	0.0083	83.65	952.23
2	120	4.84	747.68	0.0047	146.19	1325.57
3	60	4.25	262.68	0.0238	29.14	305.56
4	180	7.75	937.20	0.0226	30.70	1025.79
5	120	6.76	727.95	0.0139	49.75	819.10
6	60	5.55	388.88	0.0129	53.72	480.33
Mean	110	5.77	628.80	0.0144	65.53	818.10
SD**	60-120	1.28	251.80	0.0076	44.18	372.95

** T_{max} presented as minimum-maximum
NC = Not calculable

TABLE 13. CBD Pharmacokinetic Parameters: Pressurised Aerosol

Subject	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (min*ng/ml)	K_{el} (1/min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (min*ng/ml)
1	45	1.38	179.85	NC	NC	NC
2	120	2.76	536.85	0.0082	84.39	665.90
3	60	2.39	81.18	NC	NC	NC
4	360	4.85	940.80	0.0108	63.92	1062.52
5	120	1.61	216.90	0.0024	283.00	706.84
6	NC	NC	0.00	NC	NC	NC
Mean	141	2.60	325.93	0.0071	143.77	811.75
SD**	45-360	1.38	352.68	0.0043	121.01	218.13

** T_{max} presented as minimum-maximum
NC = Not calculable

TABLE 14. THC Pharmacokinetic Parameters: Pressurised Aerosol

Subject	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (min*ng/ml)	K_{el} (1/min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (min*ng/ml)
1	180	2.43	500.10	0.0143	48.45	570.00
2	120	4.66	814.95	0.0152	45.55	888.55
3	60	3.72	356.60	0.0101	68.78	466.74
4	180	4.64	1139.40	0.0105	66.28	1263.71
5	120	3.04	377.03	0.0068	101.54	573.32
6	120	3.67	628.58	0.0041	167.41	894.25
Mean	130	3.69	636.11	0.0102	83.00	776.09
SD**	60-180	0.88	299.70	0.0043	45.93	297.88

** T_{max} presented as minimum-maximum
NC = Not calculable

TABLE 15. 11-Hydroxy THC Pharmacokinetic Parameters: Pressurised Aerosol

Subject	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (min*ng/ml)	K_{el} (1/min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (min*ng/ml)
1	180	4.32	820.43	0.0107	65.08	958.44
2	120	6.08	1380.68	0.0046	149.66	1639.78
3	60	6.03	1726.43	0.0046	149.78	2082.97
4	360	6.54	2290.50	0.0050	137.48	2490.83
5	120	7.10	1316.03	0.0043	160.82	1550.36
6	120	7.30	1875.15	0.0042	165.86	2305.87
Mean	160	6.23	1568.20	0.0056	138.11	1838.04
SD**	60-360	1.07	509.69	0.0025	37.12	565.82

** T_{max} presented as minimum-maximum
NC = Not calculable

between the pressurised aerosol and CBD:THC sublingual drops. Following dosing with the pressurised aerosol T_{max} of both CBD and THC were a little later than after dosing with the CBD:THC sublingual drops (CBD 141 vs. 100 min and THC 130 vs. 100 min). CBD C_{max} was very similar but AUC_{0-t} and $AUC_{0-\infty}$ were greater than following CBD:THC sublingual drops whereas THC C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were all less than the sublingual drops. None of these differences was statistically significant.

Inhaled Nebuliser

The dose administered via the inhaled nebuliser was approximately half that of the sublingual drops and aerosol. T_{max} of both CBD (36 min) (Table 16) and THC (32 min) (Table 17) were much earlier than the corresponding values after the sublingual drops (100 min and 100 min, respectively) or aerosol (T_{max} THC = 130 min, CBD = 141 min), though only the difference in THC T_{max} was significant for sublingual drops ($p = 0.0046$). Mean C_{max} of CBD (9.49 ng/ml) was statistically significantly greater than for the CBD:THC sublingual drops (2.58 ng/ml) ($p = 0.0104$). Mean C_{max} of THC was similarly greater (12.46 vs. 6.5 ng/ml) though the difference was not statistically significant. Mean AUC_{0-t} of CBD (564.35 ng/ml.min) was greater than for the CBD:THC sublingual drops (209.30 ng/ml.min); however, with a p-value of 0.0529, this was not a statistically significant difference. The AUC_{0-t} and $AUC_{0-\infty}$ values for CBD following dosing with the inhaled nebuliser were greater, though not statistically significantly, than the correspond-

TABLE 16. CBD Pharmacokinetic Parameters: Nebuliser

Subject	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (min*ng/ml)	K_{el} (1/min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (min*ng/ml)
1	5	22.62	442.55	0.0275	25.23	479.68
2	30	9.87	499.53	0.0166	41.70	587.36
3	45	2.74	219.60	0.0039	179.66	750.96
4	15	4.70	171.20	0.0278	24.92	235.20
5	60	14.75	1859.90	0.0124	55.69	1997.28
6	60	2.25	193.33	0.0103	67.05	310.36
Mean	36	9.49	564.35	0.0164	65.71	726.81
SD**	5-60	8.01	649.39	0.0096	58.25	649.66

** T_{max} presented as minimum-maximum
NC = Not calculable

TABLE 17. THC Pharmacokinetic Parameters: Nebuliser

Subject	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (min*ng/ml)	K_{el} (1/min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (min*ng/ml)
1	5	25.85	633.30	0.0334	20.74	675.50
2	30	14.74	884.58	0.0144	48.18	963.81
3	60	3.73	449.63	0.0089	77.77	593.24
4	30	5.15	217.35	0.0191	36.21	368.84
5	5	21.97	2256.68	0.0164	42.21	2387.60
6	60	3.29	276.48	0.0120	57.69	409.64
Mean	32	12.46	786.33	0.0174	47.13	899.77
SD**	5-60	9.89	760.53	0.0086	19.45	759.49

** T_{max} presented as minimum-maximum
NC = Not calculable

ing values for CBD:THC sublingual drops. $AUC_{0-\infty}$, AUC_{0-t} , C_{max} and T_{max} for 11-hydroxy-THC (495.67 ng/ml.min, 65.15 ng/ml.min, 1.65 ng/ml and 38 min, respectively) (Table 18) were statistically significantly lower when compared to the CBD:THC sublingual drops (2066.30 ng/ml.min, 1842.75 ng/ml.min, 8.25 ng/ml and 140 min, respectively). The p-values were 0.0034, < 0.0001, < 0.0001 and 0.0054, respectively.

Analysis of Cognitive Assessments and Well-Being

For each test treatment period, subjects were required to undertake a battery of cognitive assessments (Periods 1 to 4 only) and complete a well-being questionnaire. Subjects were also required to report a series

TABLE 18. 11-Hydroxy THC Pharmacokinetic Parameters: Nebuliser

Subject	T_{max} (min)	C_{max} (ng/ml)	AUC_{0-t} (min*ng/ml)	K_{el} (1/min)	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (min*ng/ml)
1	10	1.56	30.10	NC	NC	NC
2	45	1.18	25.65	NC	NC	NC
3	NC	NC	0.00	NC	NC	NC
4	NC	NC	0.00	NC	NC	NC
5	60	2.21	270.00	0.0052	132.56	495.67
6	NC	NC	NC	NC	NC	NC
Mean	38	1.65	65.15	0.0052	132.56	495.67
SD**	10-60	0.52	115.37	NC	NC	NC

** T_{max} presented as minimum-maximum
NC = Not calculable

of well-being parameters using visual analogue scales (VAS). Each pre-dose assessment was taken to be the baseline measurement for each well-being parameter for each period.

Wakefulness was rated (0 = very drowsy and 100 = fully alert). CBD:THC sublingual drops resulted in the greatest drop in feeling of wakefulness with a decrease in wakefulness of -32.5 from baseline (88.5) at 3 h post-dose. All other test treatments, with the exception of placebo, which showed increased wakefulness throughout, also showed the greatest effect on wakefulness at 3 h post-dose with a range of decreases of -11.5 (High CBD) to -20.2 (aerosol).

Well-being was rated (0 = feel terrible and 100 = feel wonderful). Each test treatment resulted in a reduction similar to that for placebo in feeling of well-being. The greatest reduction (14.2 relative to baseline (94.0) at 3 h post-dose) was as a result of the CBD:THC sublingual drops. High CBD resulted in a later (-4.0 relative to baseline at 8 h post-dose) maximum mean decrease and the aerosol test treatment resulted in an earlier (-2.3 relative to baseline at 10 min post-dose) maximum mean decrease.

Mood was rated (0 = feel terrible and 100 = feel wonderful). All test treatments resulted in a maximum mean decrease (-2.2 to -11.3 relative to baseline) in mood at 3 h post-dose with the exception of the aerosol test treatment which showed a maximum mean decrease (2.7 relative to baseline) at 8 h post-dose.

Dry mouth was rated (0 = very dry and 100 = normal moisture). All test treatments, with the exception of the inhaler, resulted in a maximum mean increase in reporting of dry mouth at 3 h post-dose. CBD:THC

sublingual drops resulted in the greatest increase in dryness of mouth with a maximum mean of -48.7 relative to baseline. The nebuliser test treatment resulted in an earlier maximum mean decrease with a change of -10.8 (relative to baseline) at 10 min post-dose.

Hunger was rated (0 = very hungry and 100 = not hungry). All test treatments and placebo resulted in a maximum mean increase in reported feeling of hunger at 3 h post-dose. The range of change from baseline was -9.8 (CBD:THC sublingual drops) to -27.5 (aerosol). The maximum mean increase in hunger following the placebo dose was -16.0 .

Unpleasant effects were rated (0 = very unpleasant effects and 100 = no unpleasant effects). The maximum mean (relative to baseline) reporting of unpleasant effects was varied for each test treatment. CBD:THC sublingual drops was -11.5 at 3 h post-dose, High CBD was -9.3 at 12 h post-dose, High THC was -4.5 at 10 min post-dose, the aerosol was -5.7 at 8 h post-dose and the nebuliser was -14.0 at 10 min post-dose. The placebo treatment also resulted in reporting of unpleasant effects with a maximum mean increase of -6.5 at 10 min post-dose.

Post-Study Questionnaire

The results of the post-study questionnaire were assessed descriptively using frequency tables for each treatment. All of the subjects reported that the test treatment liked best was the 'liquid under the tongue' and the least liked test treatment was the nebuliser. Half of the subjects reported that the CBD:THC sublingual drops had the most pleasant effects and 67% (4) of the subjects reported that the nebuliser had the least pleasant effects. All of the subjects reported coughing and half reported a sore throat after administration of the test treatment via the nebuliser.

Analysis of Safety Parameters

The output from the cardiac monitors was intended for use at the clinical unit as an ongoing assessment for each subject. No concerns were raised as a result of the cardiac monitoring.

Pre-dose, all test treatments, including placebo but with the exception of High CBD, had between one and three subjects (17-50%) reported as having slight conjunctival reddening. Pre-dose High CBD, no conjunctival reddening was reported. Post-dose for all test treatments including placebo, the majority of subjects (67-100%) were reported as having 'slight' or 'no' conjunctival reddening. With the exception of

High CBD, moderate conjunctival reddening was reported in a maximum of two subjects (33% between 31 min and 4 h 01 min) for all test treatments including placebo. Only one subject had severe conjunctival reddening (on CBD:THC sublingual drops at 4 h 01 min).

Blood Pressure and Pulse During Treatment Periods

For each of the BP and pulse, parameters descriptive statistics (N, mean, SD, median, minimum and maximum) and the changes from pre-dose baseline were presented at each time point by test treatment group. In addition, the summaries were assessed for the absolute change from pre-dose.

12-Lead ECG

The ECG assessments (normal/abnormal) were assessed pre- and post-study.

Drug Dose, Drug Concentration and Relationships to Response

Each subject received three single doses of CBD:THC (20 mg CBD + 20 mg THC), one single dose of High THC (20 mg THC) and one single dose of High CBD (20 mg High CBD) (Table 19). The maximum total dose that was planned to be administered in the study was 80 mg CBD and 80 mg THC.

Drug-Drug and Drug-Disease Interactions

This study was carried out in healthy subjects who were not taking any medication.

Plasma Concentration Conclusions

Sublingual Drops

Following co-administration of CBD and THC as sublingual drops, mean concentrations of CBD, THC and 11-hydroxy-THC were above the LLOQ by 45 min post-dose. Plasma concentrations of THC were at least double those of CBD before both decreased below the LLOQ by 360 min and 480 min post-dose, respectively.

When High CBD sublingual drops were administered, plasma levels of CBD were generally similar to those measured after CBD:THC sublingual drops.

TABLE 19. Total Dose of Test Treatment Administered to Each Subject

Subject	Test Treatment					
	CBD:THC SL Drops	Placebo	High CBD SL Drops	High THC SL Drops	Aerosol	Nebuliser
1	20 mg CBD + 20 mg THC	0 mg	20 mg CBD	20 mg THC	20 mg CBD + 20 mg THC	2.5 mg CBD + 2.5 mg THC
2	20 mg CBD + 20 mg THC	0 mg	20 mg CBD	20 mg THC	20 mg CBD + 20 mg THC	2.5 mg CBD + 2.5 mg THC
3	12.5 mg CBD + 12.5 mg THC	0 mg	20 mg CBD	15 mg THC	20 mg CBD + 20 mg THC	2.5 mg CBD + 2.5 mg THC
4	20 mg CBD + 20 mg THC	0 mg	20 mg CBD	20 mg THC	20 mg CBD + 20 mg THC	2.5 mg CBD + 2.5 mg THC
5	20 mg CBD + 20 mg THC	0 mg	20 mg CBD	20 mg THC	20 mg CBD + 20 mg THC	0 mg**
6	20 mg CBD + 20 mg THC	0 mg	20 mg CBD	20 mg THC	20 mg CBD + 20 mg THC	0 mg**

** Subjects 005 and 006 received a placebo dose via the nebuliser

High THC resulted in mean levels of both THC and 11-hydroxy-THC being above the LLOQ earlier and also resulted in a slightly earlier decline than for CBD:THC. However, the concentrations of THC and 11-hydroxy-THC in plasma were similar or a little lower.

Pressurised Aerosol

Following administration of CBD:THC via the pressurised aerosol, mean levels of CBD and THC above the LLOQ were detected a little earlier than for the CBD:THC sublingual drops and declined below the LLOQ a little later. Plasma concentrations of THC, 11-hydroxy-THC and CBD were lower than following the sublingual drops.

Nebuliser

Following a dose administration of CBME via the nebuliser of approximately half that of the sublingual drops, mean plasma levels of both CBD and THC rose rapidly (within 5 min) to levels much higher than measured following sublingual drops and were maintained until around 120 min post-dose before declining rapidly. Levels of 11-hydroxy-THC were very low compared with those after sublingual dosing.

In conclusion, following sublingual administrations of CBD alone, THC alone or CBD:THC combined there was little difference in the plasma concentrations of THC or CBD. However, plasma levels of

CBD are less than corresponding levels of THC suggesting lower bioavailability. Following administration of CBD and THC by pressurised aerosol blood levels of both THC and CBD were lower compared with the sublingual drops. Following administration of CBD and THC via the nebuliser, there was rapid absorption and much greater plasma levels of both CBD and THC compared with sublingual dosing and the low levels of 11-hydroxy-THC suggests that metabolism of THC was significantly reduced.

Pharmacokinetic Conclusions

There were no statistically significant differences in the PK of THC or CBD between CBD:THC sublingual drops and High THC, High CBD or pressurised aerosol. With the exception of a single statistically significant difference in $AUC_{0-\infty}$ for 11-hydroxy-THC following administration of the High THC compared with CBD:THC sublingual drops there were no significant differences in the PK of 11-hydroxy-THC either. The differences in plasma concentrations and mean PK parameters observed between some of these treatments in the study were small relative to the individual variability.

Dosing with the inhaled nebuliser produced marked differences in the PK of CBD and THC compared with CBD:THC sublingual dosing. Peak concentration was greater and much earlier although only C_{max} of CBD and T_{max} of THC were statistically significantly different. Peak concentration and AUCs of 11-hydroxy-THC were statistically significantly less, reflecting reduced early metabolism of THC by this route.

In conclusion, no consistent statistically significant differences were noted between the PK parameters of High CBD, High THC and the aerosol when compared to the CBD:THC sublingual drops. However, the nebuliser resulted in a rapid absorption of CBD and THC and higher peak plasma levels but a reduction in the metabolism of THC to 11-hydroxy-THC.

Well-Being Conclusions

Results indicate that subjects experienced changes in wakefulness, feeling of well-being, mood, production of saliva and increased hunger and unpleasant effect. These were not clinically different following administration of each test treatment or placebo. The maximum mean reduction in wakefulness, feeling of well-being, mood and production of

saliva were reported at 3 h post-dose and were as a result of CBD:THC sublingual drops.

Only small insignificant changes in wakefulness, feeling of well-being and mood were reported following administration of the placebo test treatment. However, a similar decrease in production of saliva, increase in hunger and marginally smaller incidence of unpleasant effects were seen with CBD:THC sublingual drops.

The greatest mean increase in hunger was reported following administration of the aerosol test treatment at 3 h post-dose. However, a similar effect was also observed at 3 h post-dose following administration of the placebo test treatment.

The greatest mean incidence of unpleasant effects was reported earlier than for any other effect and following administration of the nebuliser test treatment.

In conclusion, the decrease in general feeling of well-being were greatest following administration of CBD:THC sublingual drops.

Post-Study Questionnaire Conclusions

The sublingual test treatments were best liked and the nebuliser test treatment was least liked. The effects experienced following test treatment administration via the nebuliser were least liked. All of the subjects reported coughing and three subjects reported a sore throat following dosing during dosing with the nebuliser.

SAFETY EVALUATION

All six subjects completed all six periods of study treatment. The actual doses administered are presented in Table 19.

ADVERSE EVENTS

Brief Summary of Adverse Events

All six subjects experienced at least two AEs each during the study (Table 20). All the AEs were non-serious and most (32 events) were related to the study treatment. The majority of AEs were mild or moderate in intensity and only three AEs were severe. Only one AE was persisting at the end of the study, and most of the events that resolved did so

TABLE 20. Number and Severity of AEs by Test Treatment

Test Treatment	Number and Severity of AEs			Total
	Mild	Moderate	Severe	
THC:CBD SL drops	3	6	2	11
High CBD SL drops	1	4	1	6
High THC SL drops	5	6	0	11
Placebo	1	2	0	3
Aerosol	4	4	0	8
Nebuliser	1	5	0	6
Total	15	27	3	45

without treatment (35 events). The AEs experienced were abnormal dreams, conjunctival hyperaemia, tachycardia, pallor, sleep disorder, increased sweating, hot flushes, hyperacusis, upper abdominal pain, frequent bowel movements, increased body temperature, hunger, depressed mood, cough and hypotension.

Table 20 summarises the number and severity of AEs by test treatment.

Analysis of Adverse Events

All six subjects experienced at least two AEs each during the study. All the AEs were non-serious. Most AEs were related to the study treatment in the active groups, but more AEs were unrelated to treatment in the placebo group. The majority of AEs were mild or moderate in intensity. Only three AEs out of a total of 45 were severe and occurred when the subjects were receiving CBD:THC sublingual drops (conjunctival hyperaemia and hunger) and High CBD sublingual drops (conjunctival hyperaemia). Only one AE was persisting at the end of the study (menopausal symptoms in a 43-year-old female subject, not related to treatment), and most of the events that resolved did so without treatment.

Although the number of patients was small, there were differences between the active study treatments and placebo. Only one subject developed an AE following administration of placebo whereas three to four subjects developed AEs following administration of the active test treatments. Tachycardia, conjunctival hyperaemia and abnormal dreams were the most common AEs experienced and accounted for three, five and eight AEs, respectively, across all treatment groups. Tachycardia

was the most common AE in subjects receiving High THC sublingual drops (two subjects); conjunctival hyperaemia was the most common AE in subjects receiving CBD:THC sublingual drops (two subjects); and abnormal dreams was the most common AE in subjects receiving the aerosol (two subjects) and the inhaler (two subjects). Conjunctival hyperaemia and abnormal dreams were the jointly the most common AEs in subjects receiving the nebuliser.

Abnormal dreams was the only intoxication-type AE developed by the subjects during this study. At least one subject developed them while receiving any one of the test treatments (including placebo), and four subjects developed them overall. Apart from one subject who experienced a cough during the use of the inhaler, no subjects developed any AEs that may have been related to application of the test treatment. There were no deaths, SAEs or other significant AEs during this study.

CLINICAL LABORATORY EVALUATION

Laboratory Values Over Time

The mean value of each laboratory parameter exhibited only small variations from screening to post-study. The small variations did not suggest any patterns or trends.

Individual Subject Changes

Shift tables showed no more than two shifts between categories (low, normal and high) per parameter. The small number of changes did not suggest any patterns or trends.

Individual Clinically Significant Abnormalities

There were no clinically significant abnormalities in the laboratory parameters for any subject at either screening or post-study. Subject 002's urine was positive for nitrites at screening which was considered to be a clinically relevant abnormal result. There were no other clinically relevant abnormal results.

Vital Signs, Physical Findings and Other Observations Related to Safety

The mean values of all the vital signs showed no patterns or trends and no differences from placebo. ECGs at both screening and post-study were normal for all subjects.

Conjunctival Reddening

All test treatments, including placebo but with the exception of High CBD, had a reported incidence of 17-50% of slight conjunctival reddening pre-dose. Pre-dose High CBD, no conjunctival reddening was reported. Post-dose for all test treatments including placebo, the majority of subjects (67-100%) were reported as having 'slight' or 'no' conjunctival reddening. With the exception of High CBD, moderate conjunctival reddening was reported in a maximum of two subjects (33% between 31 min and 4 h 01 min) for all test treatments including placebo. Only CBD:THC sublingual drops resulted in one subject having severe conjunctival reddening at 4 h 01 min.

Safety Conclusions

The sublingual test treatments were well tolerated by all subjects. Each of the 6 subjects experienced at least two non-serious AEs during the study, but there were no deaths, SAEs or other significant AEs. There were a total of 45 AEs, the vast majority of which were mild or moderate in intensity, only three being severe. All but one AE resolved (non-related), most (35) without treatment. Most AEs were related to the study treatment, except for subjects receiving placebo where more AEs were unrelated to treatment.

The commonest AEs were abnormal dreams, conjunctival hyperaemia and tachycardia. Abnormal dreams was the only intoxication-type AE developed by the subjects during this study and was the most common AE overall. No subjects developed any AEs that may have been related to administration of the sublingual test treatments.

The small variations in individual subject laboratory parameters and urinalyses and in the mean laboratory parameters did not suggest any patterns or trends. The mean values of all the vital signs showed no patterns or trends either and no differences from placebo. ECGs at both screening and post-study were normal for all subjects.

DISCUSSION AND OVERALL CONCLUSIONS

The sublingual test treatments were well tolerated at the doses administered by all subjects. All six subjects experienced at least two non-serious AEs during the study, but there were no deaths, SAEs or other significant AEs. All but one AE resolved without treatment. Although the number of AEs was small, subjects clearly developed more AEs when receiving the active test treatment than when receiving placebo.

No overall statistically significantly different differences were reported between each of sublingual test treatments when compared to the CBD:THC sublingual drops. However, there were few subjects in this study and due to the low concentrations of cannabinoids in plasma some PK parameters could not be calculated for some subjects.

When CBD and THC are co-administered as sublingual drops, the rate of appearance of THC is marginally increased compared to being administered as High THC suggesting that CBD may stimulate the absorption of THC. The appearance of 11-hydroxy-THC is reduced when CBD and THC are co-administered suggesting that the metabolism of THC to 11-hydroxy-THC may be reduced by CBD. THC is more extensively absorbed than CBD and no changes were seen for any sublingual drop test treatments relative to CBD:THC sublingual drops.

Administration of CBD:THC via the pressurised aerosol resulted in a slightly faster rate of absorption of CBD and THC than for the CBD:THC sublingual drops. However, overall AUCs were reduced for THC and 11-hydroxy-THC and increased for CBD.

The nebuliser resulted in a very rapid rate and relatively large extent of absorption of both CBD and THC. However it also resulted in the greatest number of adverse effects experienced by the subjects. Administration of the test treatment via the nebuliser was considered practical however, the concept of administering the test treatment via the lungs was shown to be more effective than for sublingual administration. Very low concentrations of 11-hydroxy-THC were produced following nebuliser administration indicating a reduction in metabolism of THC to 11-hydroxy-THC.

Each test treatment resulted in a reduction in subjectively assessed general well-being with the greatest effects reported following administration of CBD:THC sublingual drops. Maximum effects were experienced at approximately the same time post each dose and some effects were also reported following administration of placebo. This suggests that some of the changes in feeling of well being may be due to the excipients or a placebo effect.

The reported increase in hunger following administration of each test treatment was not unexpected as maximum hunger was reported close to lunch time. The greatest mean incidence of unpleasant effects was reported earlier than for any other effect and following administration of the nebuliser test treatment.

In conclusion, each sublingual test treatment was well tolerated by all subjects. The inhaled test treatment was not well tolerated and resulted in adverse effects.

REFERENCES

- Aguirell, 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 marijuana 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.