Pilot study:
the effect of cannabis based
medicine on cognitive performance

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medicine on cognitive performance

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This pilot study was undertaken to make a provisional assessment of the effect of cannabis on cognitive function, in particular in how the ability to perform day to day tasks at work and at leisure is affected. It is important to investigate this both in terms of recreational users and for the sake of future patients taking medicinal cannabis, should appropriate regulatory approval be granted. The medicinal cannabis is an extract from contamination-free plants grown under controlled conditions. It is therefore comparable to some degree to the illegally available cannabis used recreationally although the medicinal form is not smoked but taken as a liquid under the tongue.

Six healthy volunteer subjects received a single dose on separate occasions of three preparations of cannabis and a matching placebo. Before and at certain times after the dose the subjects took a series of tests using a touch-screen computer, to measure change in cognitive function.

Overall the effects on cognitive function were minor.

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LIST OF ABBREVIATIONS

Abbreviation	Full term
CBD	Cannabidiol
CBME	Cannabis Based Medicine Extract
MOT	Motor Screening
NART	National Adult Reading Test
PAL	Paired Associates Learning
PRM	Pattern Recognition Memory
RTI	Reaction Time
RVP	Rapid Visual Information Processing
SSP	Spatial Span
SWM	Spatial Working Memory
THC	Delta 9 Tetrahydrocannabinol
ANOVA	Analysis of variance

SUMMARY

The Health and Safety Executive commissioned GW Pharmaceuticals Ltd to undertake a preliminary assessment of the effects, tolerability and safety of medicinal cannabis in healthy subjects. The main assessment was on the effect on cognitive function. This was the first administration into man of the cannabis based medicine extracts (CBME) produced by GW Pharmaceuticals Ltd.

Three CBME were administered, distinguished by the ratio between two main cannabinoids, delta 9 tetrahydrocannabinol (THC) and cannabidiol (CBD). A placebo was included for comparison. Street cannabis is valued in recreational use for its content of THC, the psychoactive component. THC is also considered to be mainly responsible for the analgesic effect of cannabis, but CBD is thought to have a modulating effect on the action of THC. This effect may prove significant in medicinal use.

All treatments were administered as sublingual drops. It was expected that delivery by this route would be somewhat slower than by smoking (the preferred recreational route, clearly unsuitable for a medicine) but markedly faster than by the oral route. In other respects the comparison to the recreational form is relatively close, as CBME are produced from contamination-free plants grown under controlled conditions (to have pre-determined content of cannabinoids) and contain other components of the plant as well as the cannabinoids. The extracts are not of isolated cannabinoids or chemically synthesised versions.

Six healthy volunteer subjects completed the study. Subjects had some experience of cannabis but were not currently chronic users. A single dose of the allocated CBME or matching placebo was administered in each of four periods. The dose was administered incrementally, allowing discontinuation at any time if the effects became unacceptable. Among other assessments, a battery of cognitive tests was undertaken pre-dose, at ten minutes after the final dose increment, and at three hours and eight hours. Five of the six subjects reported feeling 'high' or 'very high' with both of the active CBME which contained a high ratio of THC. The subjects may therefore be considered in broad terms to have had the equivalent to a moderate recreational dose, which is expected to be markedly higher than a medicinal dose required for the majority of patients. There were no on-going safety concerns.

Overall the effect on cognitive function was not marked, and only rarely reached statistical significance. However, it should be noted that the small number of subjects in the study limited the statistical power. The purpose of this probe study was to identify areas where further detailed work might be undertaken, rather than to provide a stringent statistical analysis.

The most marked deleterious effect was a decrease in performance of spatial working memory at three hours after dose (associated with THC) in comparison to placebo. This test is concerned with a central example of executive function, that is the ability to organize the information stored in the short term memory in order to organise action. This function makes a vital contribution to the way behaviour is organised and relates to problem–solving ability, the induction of strategy in novel situations and, for example, the overriding of habitual but inappropriate responses. No impairment was apparent in the tests of paired associate learning or pattern recognition memory, which are two contrasting measures of memory, fundamental to other cognitive ability. However, mild trends in impairment were apparent in results for the reaction time (associated with THC) and vigilance tasks (associated with CBD). Application of these trends is relevant across a broad spectrum of tasks and functions, and is not only of concern in terms of the speed and efficiency in performance of tasks at home and in the work place but in terms of safety to self and others in driving or use of machinery and equipment

CHAPTER 1   INTRODUCTION

1.1   THE EFFECTS OF CANNABIS ON COGNITIVE FUNCTION

1.1.1   Cannabinoid Receptors

Over the last decade or so the cannabinoid receptors CB1 and, more recently, CB2 have been identified (Matsuda et al, 1990). CB1 receptors are found in the central nervous system. In the brain they are distributed in discrete areas concerned with motor activity and postural control, memory and cognition, emotion, sensory perception and autonomic and endocrine functions. CB2 receptors are found on particular blood cells (macrophages) and in the spleen and mediate the immunological effects of cannabinoids. Notably, these receptors are absent from the brain stem, thus possibly explaining the absence of cannabis-related respiratory depression, a classic side effect of the opioids (a fact with advantageous implications for clinical use). Both CB1 and CB2 receptors are found in the peripheral tissues.

Naturally occurring chemical messengers which activate CB1 and CB2 receptors ('endogenous cannabinoid receptor agonists') have recently been discovered (Abood and Martin, 1996). In animals these have been observed to exert many of the effects of the psychoactive exogenous cannabinoids. Despite these advances in knowledge, the detailed mechanism of action of the cannabinoids remains unclear. Current thinking suggests that both CB receptors and anandamide (an endogenous receptor agonist) reside within neuronal membranes and influence intraneuronal events to modulate the excitability and responsiveness of neurons.

Certain cannabinoids, particularly THC, are psychoactive and cannabis is used recreationally for this reason. The main effect is euphoria. Cannabis however affects the brain in other ways and also affects almost every other body system to a greater or lesser degree and in a variety of ways. The development of medicinal cannabis products will aim to maximise the beneficial potential and minimise the psychoactive and other undesirable effects.

1.1.2   Cognitive Function

Evidence for brain damage associated with long-term cannabis use

Cannabinoids interact with a number of other neurotransmitter receptor systems, including noradrenaline, dopamine, serotonin, acetyl-choline, GABA, histamine, opioid peptides and prostaglandins (Pertwee, 1992), but little is known about the significance of this involvement. Most experimenters have concluded that there are few, if any, irreversible effects of THC on brain chemistry (e.g. Ali et al, 1991).

Both acute and chronic cannabis use produces alterations in brain function and metabolism in humans as measured by the electroencephalograph, cerebral blood flow studies and positron emission tomography but the interpretation of these results is controversial.

A much cited air encephalography study (Campbell et al, 1971) appeared to demonstrate cerebral atrophy in a small cohort of chronic cannabis users. However this study has been extensively criticised on methodological grounds and has never been replicated. The current consensus is that there is no convincing evidence for gross neurological damage, but subtler brain dysfunction cannot be ruled out. High densities of cannabinoid receptors in the cerebral cortex and hippocampus (Herkenham et al, 1990) suggest that attentional and memory processes are likely to be particularly sensitive to cannabis consumption.

Acute effects in humans

A wide range of cognitive impairments have been reported (e.g. O'Brien, 1996) in subjects experiencing acute intoxication, including effects upon concentration, memory, motor skills, reaction time, and manual dexterity. Test deficits have been identified in perceptual tasks (Emrich et al, 1991), time estimation (Chait et al, 1985), associative ability (Heishman et al, 1989) visual information processing (Braff et al, 1981), complex reaction time (Block & Wittenborn, 1986), and vigilance (Sharma & Moskowitz, 1974).

Impairment of memory is regarded by many as the most significant cognitive effect of cannabis (Miller, 1984), especially short-term memory. Digit span tests have given inconsistent results as have measures of recognition memory, but most free recall tasks have shown deficits following cannabis use (e.g. Chait et al, 1985). Remote memory does not seem to be affected, so it is the acquisition of new information which is impaired especially under conditions of stress or distraction. Some other tests of higher cognitive function also reveal deficits during cannabis intoxication including mental arithmetic (Chait & Pierri, 1993) and associative processes (Block et al, 1992).

Chronic effects in humans

Many hundreds of studies of varying methodological quality have been carried out over the last thirty years, and these have recently been reviewed by Solowij (1998). Her conclusion is as follows: "The weight of evidence suggests that the long-term use of cannabis does not result in any severe or grossly debilitating impairment of cognitive function. There is sufficient evidence from the studies reviewed…that the long-term use of cannabis leads to a more subtle and selective impairment of cognitive functions, which include the organization and integration of complex information involving various mechanisms of attention and memory sub-processes. The evidence suggests that prolonged heavy use may lead to progressively greater impairment. It is not known to what extent such impairment may recover with prolonged abstinence. Our understanding of the long-term cognitive effects of cannabis is far from complete."

Even with the more recent research using better designs and more sensitive measures, problems of interpretation remain: sample sizes are small, premorbid differences between users and controls may have gone unrecognised, and the effects of drug withdrawal or persisting drug residues may have been influential.

Solowij's own high-quality research (Solowij et al, 1991, 1995a, b, c; Solowij, 1995d) has made use of event-related-potentials (ERP) in an auditory selective attention task. Key findings centre on parts of the waveform known as 'processing negativity' and P300. The author's conclusion is that this 'very sensitive' technique suggests that long-term users are less able to reject complex irrelevant information at an early stage of information processing. This impairment correlates with the duration of cannabis use, and may be only partially reversible even after several years of abstinence. Possible confounding variables among her subjects include age, gender, IQ, premorbid personality and cognitive capacity, motivation and anxiety.

The research literature indicates that moderate users of cannabis are unlikely to show cognitive deficits when they are not acutely intoxicated. Owing to the slow elimination of cannabinoids from the body, however, a state of chronic intoxication is likely in those who use the drug recreationally three or more times weekly, and this can be expected to result in impairment of a number of cognitive processes. What remains uncertain is whether chronic recreational cannabis use can induce subtle, long-term cognitive impairment which is only partially reversible and, if so, what the practical consequences of this might be in terms of daily living.

1.2 GW PHARMACEUTICALS Ltd

1.2.1 The Company

The company GW Pharmaceuticals Ltd was created to undertake the research and development of cannabis based medicine extracts. This project followed the findings of the House of Lords Select Committee on Science and Technology which recommended that clinical trials of cannabis for the treatment of multiple sclerosis (MS) and chronic pain be mounted as a matter of urgency and that research should be promoted into alternative modes of administration which would retain the benefits of the rapid absorption offered by smoking without the associated adverse effects (House of Lords report, 1998). GW Pharmaceuticals Ltd. will therefore assess the efficacy and safety of cannabis based medicine extracts. A major safety concern is the effect on cognitive function in the treated patient, particularly in those patients who drive, or whose employment involves the use of potentially dangerous equipment or machinery. In addition, any effect on the cognitive ability to complete any tasks, whether in employment or in the home, is of concern to the patient who may already suffer some impairment due to the medical condition.

1.2.2 Initial Research

Initial research into the effects of CBME on cognitive function will be undertaken mainly in healthy volunteer subjects rather than patients. There is a two-fold reason for this, firstly it is necessary to obtain information unprejudiced by the potentially confounding effects of the medical conditions suffered by the intended group of patients, secondly patients in a poor state of health and possibly compromised mobility would find the attendance and participation in early complex studies onerous, and should be spared these, especially where only single doses of the medication are given and no lasting benefit to the patient may be expected.

The findings of volunteer studies are of significance in the context of both recreational and medicinal use.

1.2.3 The Medication

Cannabis Based Medicine Extracts (CBME) are whole plant extracts processed from specific chemovars (varieties characterised by chemical constituent) grown under licence from the Home Office.

The precise main cannabinoid content of each chemovar is known. Plants are cloned and the cannabinoid content remains markedly consistent. Among the chemovars grown are ones with a high content of THC and ones containing a high content of cannabidiol (CBD). It is therefore possible, by combining these products, to produce extracts containing these two cannabinoids in specified ratios and amounts.

THC has long been known as the main psychoactive component of cannabis and until recently the beneficial medical effects of cannabis have been attributed to THC alone. CBD is non-psychoactive but does have analgesic effect and is believed to have a modulating effect on the actions of THC. For example, it is established that THC causes a tachycardia which may be associated with the anxiety and unease experienced by (naïve) users. CBD, however, may reduce heart rate and so a combination of these two cannabinoids may result in analgesic therapeutic benefit with fewer adverse effects (Nahas and Trouve, 1985)

The majority of unregulated cannabis available in North America is believed to be of Mexican or South American origin and strains from these regions tend to have low CBD content.

Subsequent growing from seed in North America has resulted in increasingly high THC content as the majority of (illegal) growers are motivated by the psychoactive properties of the plant. In the UK the majority of supply has been predominantly from Morocco as well as the rest of the Mediterranean countries, and Asia. Strains from these regions tend to have a markedly higher CBD content (Clarke, 1998).

These facts have interesting sequelae: the best-known medical use of cannabis in the USA has been in treating pain in cancer patients and to promote appetite in AIDS sufferers with wasting syndrome. In the UK however, although cannabis is in use in a wide variety of medical conditions, according to an ever-increasing corpus of anecdotal evidence, its most familiar use is in multiple sclerosis (MS), to treat pain and also spasm, tremor and other neurological dysfunction. There is therefore the possibility that the modulating effect of CBD on the action of THC may enhance the beneficial effect in certain clinical conditions, and certainly does reduce some of the unwanted effects. Hence it is the intention of GW Pharmaceuticals Ltd to research CBME containing different ratios of THC:CBD, and to investigate whether there is correlation between cannabinoid ratio and effect in a range of medical conditions.

Many of the early studies of cannabis were undertaken at a time before the potential importance of CBD was recognised and consequently the CBD content, and very often the precise THC content, of the material studied was not known. THC content varies greatly in the unregulated supply as well as the ratio to CBD. It is therefore very likely that variation in supply between studies has existed and this may well account for some of the discrepancies in findings between studies.

1.2.4   Administration routes

There will be difficulty in comparing the effects of studies in which the precise amounts of cannabinoids given are known, with the effect of recreational cannabis use in the unregulated user because in unregulated use:
- neither the amount of total cannabinoid nor the relationship between THC and CBD is known (both are likely to be subject to wide variability).
- the substance is most commonly taken by smoking either the herb ('grass' or 'bud') or the processed resin, or by ingesting the material in a cooked form or infusion, whereas in the clinical research setting administration routes such as the sub-lingual or the inhaled route will be utilised.
- the amount of cannabis placed into the 'joint' may be a poor guide to the amount which will be bioavailable. On-going laboratory studies undertaken by GW Pharmaceuticals Ltd indicate that the majority of the cannabinoids remain in the butt of the joint.

Comparison of effect should therefore be correlated with plasma concentration where possible.

Smoking is clearly unacceptable for medicinal products because of the associated health risk. Oral administration, although it may in the future prove appropriate for some clinical indications, has delayed bioavailability and effect and, due to metabolism by the liver, additional unwanted side effects. GW Pharmaceuticals Ltd are currently administering the drug by the sub-lingual route and in the future expect to add the option of administration by inhalation. Both these routes have the advantage of rapid effect (in relation to the oral route), and thus the drug can be given gradually, in increments, so that the patient can discontinue the dosing as soon as a beneficial effect is apparent, thereby avoiding an unnecessarily large and potentially intoxicating dose. Anecdotal evidence suggests that clinical benefit may result from a much smaller dose than that which would be required to produce a psychoactive effect, which is undesirable in the clinical setting.

1.3 INTRODUCTION TO CANTAB

1.3.1 CANTAB: The Cambridge Neuropsychological Test Automated Battery

CANTAB is a computerised battery of tests for neuropsychological evaluation, administered by a neuropsychologist, assistant psychologist, nurse, technician or equivalent. Data are stored automatically. An average subset of tests would take no longer than 40 minutes and could be as short as 20 minutes, dependent on the tests used (completion of the entire battery is not recommended, rather that the sub-tests are chosen according to the patient group and hypothesis being tested). CANTAB tests have proven sensitivity and specificity in differentiating patients with a number of neurological conditions from each other and from normal controls. All twelve tests are language free, making CANTAB highly suitable for multinational studies and when testing young, psychiatrically disturbed or cognitively-impaired subjects. Various sub-tests provide assessment of different cognitive functions including learning, memory, attention (including sustained, divided and selective forms), and tests of executive function (including problem solving and planning). The tests are graded in difficulty – avoiding floor and ceiling effects and are administered via a touch-screen, thus testing the individuals cognitive performance rather than their ability to use a computer.

1.3.2 Summary of the Main Merits of the CANTAB System

The main merits of the CANTAB system are as follows:
- easy-to-administer via a touch sensitive computer screen, portable, rapid, non-invasive. Computerisation also ensures that the tests are extremely effective for multi-centre trials given the uniform delivery system
- the battery includes a comprehensive range of cognitive tests including measures of memory, learning, attention and planning including measures of 'executive function' and vigilance
- the tests are highly specific and sensitive. That is, many of the tests are sensitive to specific brain regions including frontal or temporal lobe and connected areas, such as the basal ganglia, thus 'profiles' of performance can be shown
- language and culture free (used in 14 different countries.)
- graded in difficulty to suit a broad range of age, ability and culture, increasing test sensitivity
- resistant to practice effects for repeat testing
- demonstrates high participant compliance
- standardised and validated (in over 2000 patients and controls and increasingly in neuroimaging studies)
- customised test batteries are available
- over 120 papers published in peer reviewed journals
- the data are stored automatically and then analysed in a simple, easy to use 'downloadable' format.

1.3.3 Sensitivity to Medication

CANTAB has been shown to be highly sensitive to the effects of medication, even when traditional cognitive measures have proven insensitive. To date there are over 20 published studies to assess the effects of drug intervention in both healthy individuals and different patient groups. The tests are being increasingly utilised as sensitive and discriminative outcome measures in pharmaceutical drug trials.

1.3.4   Standardisation and Validation

CANTAB has been extensively standardised and validated and is being used in hospitals and neuroscientific research groups in 14 countries, across four continents. Over 1000 healthy controls have been tested and their data have been used to determine norms. The tests have been used in over 30 different patient groups (over 1000 patients) and increasingly in functional neuro-imaging studies. Test-retest reliability has been found to be good in the majority of tests (between 0.6 and 0.8, where 0 indicates poor reliability, and 1.0 indicates perfect reliability).

CHAPTER 2   METHODS

2.1   STUDY DESIGN

The objectives of the phase 1 pilot study were to assess the tolerability, pharmacodynamics and pharmacokinetics of three cannabis based medicine extracts (CBME) in comparison with placebo. The study was a four period, partially randomised cross-over study undertaken in a professional clinical research centre. The main pharmacodynamic investigation was to assess the effect of the medications on cognitive function, using the specialised CANTAB tests.

Prior to the study the subjects underwent a clinical screening which included recording of medical history, physical examination, demographic details and other clinical tests.

Six healthy volunteer, subjects were studied in three groups each of two subjects. The subjects had previous experience of recreational cannabis but were not currently chronic users. The CBME was administered in increments as described in Section 2.3. Each period was of seven days with dose administration on Day 1. The subjects were admitted to the unit the night before dose and remained until the morning after dose. The remainder of the period was a washout interval.

Screening for drugs of abuse and pregnancy were performed pre study and prior to dose in each period and a breathalyser test performed. Positive results from any of these tests would have caused the subject to be withdrawn from the study.

The subjects undertook the CANTAB battery of tests as follows:
- the day before dose in Period 1 as a baseline assessment.
- in each period, at 10 minutes after the final dose increment.
- at three hours after the start of dose.
- at eight hours after the start of dose.

In addition to the CANTAB tests, in each period visual analogue scales of subjective effects were recorded, vital signs and conjunctival reddening were measured and blood samples (for assay of cannabinoids) taken prior to dose and at specified times after the start of dose. Cardiac monitoring was continuous from before dose until four hours after.

A further clinical examination was undertaken at the end of the study.

2.2 STUDY OBJECTIVES

The objectives of the study were to make a preliminary evaluation of the tolerability of CBME at single dose in comparison to placebo in order to provide guidance for dosage in future research, and to compare the effects of the medication in comparison with placebo in terms of:
- cognitive assessment
- subjective assessment of well-being
- *in vivo* pharmacokinetic characteristics over 12 hours
- the adverse event profile, and other safety data.

The particular objectives of this study in terms of cognitive assessments were:
- to investigate differences between the four treatments in cognitive assessments as measured by CANTAB
- to show within each treatment which time point showed the strongest effect in cognitive assessments as measured by CANTAB

2.3 STUDY MEDICATION

The four treatments were as follows:
- CBME THC:CBD, 1:1
- CBME High THC
- CBME High CBD
- Matching placebo

All subjects received CBME THC:CBD, 1:1 in the first period. In the other three periods the allocation of treatments was in a randomised order to which both the Investigator and the subject were blind.

There was a washout interval of one week between each treatment.

The doses were given incrementally and the subject or the Investigator could discontinue the treatment at any time, should undesirable effects become apparent. The medicine was administered in increments via a fixed volume dispenser. Each increment (except for placebo) comprised THC 2.5 mg and/or CBD 2.5 mg in 0.5 ml (dependent on formulation). There was an interval of ten minutes between increments, to allow for the emergence of delayed effects. A maximum of eight increments was permitted, thus the maximum amount of active medication in any one period was THC 20 mg and/or CBD 20 mg, administered over a maximum of 70 minutes.

CHAPTER 3   CANTAB BATTERY AND ASSOCIATED ASSESSMENTS

3.1   PRE STUDY ASSESSMENTS ASSOCIATED WITH CANTAB

The National Adult Reading Test (NART)

This test was undertaken to provide a proxy measure of intelligence. The majority of words in the English language can be read and pronounced according to familiar rules, even those which are unfamiliar to the reader. There is also a subset of English words which, if pronounced according to these rules, would result in incorrect pronunciation. These 'irregular' words can only be read correctly if the subject knows and recognises them in their written form, For example, correct pronunciation of 'naïve' could not be reached without previous knowledge of the word. Therefore, reading of this type of word should provide a particularly sensitive measure of word recognition and familiarity with words.

The words appeared on the computer screen, and responses were recorded as correct pronunciation or incorrect pronunciation by the tester via the computer mouse.

The Hospital Anxiety and Depression Scale (HADS)

This test was undertaken in order to exclude subjects if found to be suffering from clinically significant anxiety or depression.

The Ishihara Colour-blindness screening test (short-form)

This test was undertaken to determine if a subject was affected by red-green colour blindness which would affect ability to undertake the tests.

3.2   CANTAB TEST BATTERY

Motor Screening (MOT)

This program runs the motor screening test which is carried out at the start of each assessment. A series of crosses is shown in different locations on the screen. After a demonstration of the correct way to point using the forefinger of the dominant hand, the subjects must point to the crosses in turn. This motor screening test has two purposes. First, it acts as a training procedure to ensure that the subjects can point accurately and use the touch-screen competently. Second, the program provides measures of both speed and accuracy that provide an index of the subjects' motor skill.

Paired Associates Learning (PAL)

This test is a form of delayed response procedure. In essence the subject is required to remember patterns associated with different locations on the screen, and during the test phase, as each pattern is presented, point to the appropriate location. The test starts at a very simple level. Six "boxes" are drawn on the screen. All are opened in a randomised order. In one of them is a pattern. After the last box has been closed the pattern is shown in the middle of the screen and the subject must point to the box where the pattern was located. If the choice is correct, the procedure is repeated with a single, new pattern. If the choice was incorrect all the boxes are reopened (the reminding phase), after which the subject must choose again.

This procedure tests two different aspects of the ability to form visuo-spatial associations. First, the number of patterns placed correctly on the first presentation of each trial gives an index of "list memory" Second, the number of repeat, reminder presentations needed for the subject to learn all the associations provides a measure of "list learning" (the task can also be conceived as a test of visuo-spatial conditional learning). The subjects may have up to ten repeat, reminder presentations with each set of patterns to learn the list. If any list has not been correctly completed within ten presentations the test is automatically terminated.

Pattern Recognition Memory (PRM)

In the CANTAB pattern recognition task the subjects are presented with twelve visual patterns in the centre of the screen. These patterns are designed so that they cannot easily be given verbal labels. In the recognition phase, the subjects are required to choose between a pattern they have already seen and a novel pattern. In the recognition phase the test patterns are presented in the reverse order to the original order of presentation.

For the delayed recognition version, 12 patterns are shown one at a time. This time, the recognition phase comes approximately 30 minutes later. Again, two patterns are shown, and the subject has to touch the one seen before.

Rapid Visual Information Processing (RVP)

The RVP is a test of sustained attention with a small working memory component. A white box appears in the centre of the computer screen, inside which digits from 2 to 9 appear in a pseudo-random order, at the rate of 100 digits per minute. The test lasts for 4 minutes though the first minute is not scored and so acts as a 'warm-up' period. Subjects are requested to detect consecutive odd or even sequences of digits (e.g. 2-4-6, 3-5-7, 4-6-8, 5-7-9, etc.) and to register responses with a button press. Target sequences occur at the rate of 16 every 2 minutes. For scoring purposes CANTAB calculates the number of responses recorded as having occurred within 1800msec of the final digit presentation for each of the target sequences. CANTAB also records the number of false alarms, i.e. the occasions when the subject incorrectly identified a target sequence. Finally, CANTAB also records and reports the mean hit response latency.

Reaction Time (RTI)

This test features versions of classic simple reaction time and 5-choice reaction time. In the simple reaction time task, the subject has to hold the press-pad down, then release it and touch the screen when a yellow dot appears in the centre, neither touching too soon or too late. In the choice reaction task, the yellow dot may appear in any one of 5 locations.

The task is divided into practice and test components. Subjects are required to reach a criterion level of at least 9 out of 10 correct responses in the practice block before being presented with the test block. If subjects fail to reach criterion in the first practice block then a second block of practice is given. After a second block of practice, the task proceeds to the test block irrespective of how well the subject has performed. This has 15 trials.

Spatial Span (SSP)

The program tests the subject's spatial memory span. A pattern of white squares is shown on the screen. Some squares change in colour, one by one, in a variable sequence. At the end of the presentation of each sequence a tone sounds. The subject then touches each of the boxes coloured by the computer in the same order as they were originally presented. The number of boxes in the sequence is increased from two at the start of the test to a final level of nine There are three sequences at each level. If the subject is unable to repeat all three sequences at any one level, the test is then terminated. The sequences and colours used are changed to minimise interference.

Spatial Working Memory (SWM)

In this test a trial begins with a number of coloured squares (boxes) being shown on the screen. The overall aim is that the subject should find a blue "token" in each of the boxes and use them to fill up an empty column on the right hand side of the screen. The subject must touch each box in turn until one opens with a blue "token" inside (a search). Returning to an empty box already sampled on this search is an error.

When the blue "token" has been found, the subject has to place it in the right column ("black hole") by touching the right hand side of the screen. The box that contained the blue "token" will not contain another blue "token" on this trial. Returning to this box is also an error. The subject must then begin a new search for the next blue "token". It may be in any of the boxes that so far have been empty. The order in which the subject searches the boxes is determined by the subjects themselves, but the number of empty boxes they must visit (discounting errors) is determined by the computer. At the end of each trial, when the column is full, a 'COMPLETE' message is displayed followed shortly afterwards by the message 'NEW SET'.

The number of boxes is gradually increased until it is necessary to search a total of eight boxes. The colour and position of the boxes used are changed from trial to trial to discourage the use of stereotyped search strategies.

3.3   CANTAB OUTCOME MEASURES

3.3.1   List of Outcome Measures

The CANTAB outcome measures assessed were:
- PAL Total Errors (adjusted).
- PAL Stages Completed.
- PAL Total Trials (adjusted).
- RTI Simple Reaction Time.
- RTI Five-Choice Reaction Time.
- RVP Total Hits.
- RVP Total False Alarms.
- RVP Mean Latency.
- SSP Span Length.
- SWM Between-errors.
- SWM Between-errors (6 boxes).
- SWM Between-errors (8 boxes).
- SWM Within-errors.
- SWM Strategy.
- SWM Total Errors.

The CANTAB outcome measures assessed as secondary variables were:
- PRM Number Correct, immediate.
- PRM Number Correct, delayed.

3.3.2   Descriptions of Tests and Outcome Measures

PAL Total errors (adjusted)

Errors are made in PAL when the subject selects a box that does not contain the target stimulus. This metric reports the total number of such errors with an adjustment for each stage not attempted due to previous failure. This adjustment is calculated by summing the number of patterns not attempted and subtracting the number of patterns divided by the number of boxes from it. This result is then multiplied by ten.

PAL Total trials (adjusted)

This measure represents the total number of presentations required (maximum score = 10 presentations per trial) to locate all the patterns correctly in all trials. When using this measure it is important to analyse the data with reference to the PAL Sets completed score. This is because subjects who fail to complete the test will have had fewer Total trials simply because they had less opportunity to make errors than subjects who completed the test. One possible way of dealing with this is to add the maximum score of 10 trials for each stage not attempted due to an earlier failure and this is what this metric shows.

PAL Stages completed

This total is the key indicator of the subject's overall success, recording how many stages were successfully completed. When analysing other outcome measures from PAL it is crucial that analyses are conducted with reference to the number of stages completed. Clearly a subject that fails prior to the successful completion of 8 box problems will have had less opportunity to make errors than a subject who completes the test.

PRM Number correct (immediate and delayed)

This measure records the number of correct responses (out of a maximum of 12) in each of the immediate and delayed versions.

PRM Mean correct latency (immediate and delayed)

The mean time to respond correctly. Latency is scored in milliseconds.

RTI Simple reaction time

A record of the speed with which the subject releases the press pad in response to the onset of a stimulus in a single location. Reaction time latency is measured in milliseconds and tends toward a positive skew. Latencies in five-choice reaction time are reliably observed to be longer than in simple reaction time. It should be remembered that subjects engaged in these tasks have the opportunity to make a variety of errors, mostly are errors of commission ('too soon', 'inaccurate' and 'wrong circle'), but errors of omission are also possible due to lack of response ('too late').

RTI Simple movement time

A record of the time taken to touch the stimulus after the press pad has been released in trials where stimuli appear in one location only. Movement time latency is usually normally distributed.

RTI Five-choice reaction time

A record of the speed with which the subject releases the press pad in response to a stimulus in any one of five locations. Latency is measured in milliseconds and tends toward a positive skew. Five-choice reaction time latencies are reliably observed to be longer than simple reaction time. Subjects engaged in reaction time tasks have the opportunity to make a variety of errors. Most are errors of commission ('too soon', 'inaccurate' and 'wrong circle'), but it is possible to make an error of an omission by not responding ('too late').

RTI Five-choice movement time

A record of the time taken to touch the stimulus after the press pad has been released in trials where one of five possible different stimuli have been presented. Movement time latency is usually normally distributed for correct responses.

RVP Total hits

This is a measure of the number of occasions upon which the target sequence is correctly responded to (within a response window of 1800 milliseconds for the clinical set-up). This score is calculated from blocks 2, 3 and 4 only.

RVP Total misses

A record of the number of occasions the subject fails to respond to a target sequence within the response window. This score is calculated from blocks 2, 3 and 4 only.

RVP Total False Alarm

A record of the number of times the subject responds outside the response window of a target sequence. This score is calculated from blocks 2, 3 and 4 only.

RVP Total Correct rejection

A record of the number of stimuli that were correctly rejected, i.e. the number of stimuli that were not part of a target sequence and were not responded to. This score is calculated from blocks 2, 3 and 4 only.

RVP Mean Latency

This is the mean time taken to respond and is reported in milliseconds. It only includes correct responses made within the response window of 1800 milliseconds.

SSP Span Length

A record of the longest sequence successfully recalled by the subject (the subject has three attempts at each level).

SWM Between-errors

'Between-errors' are defined as times the subject revisits a box in which a token has previously been found. This is calculated for trials of four or more tokens only.

SWM Within-errors

'Within-errors' are defined as the number of errors made within a search, i.e. the number of times a subject revisits a box already found to be empty during the same search. This is calculated for trials of four or more tokens only.

SWM Total errors

A record of the number of times selection is made of a box that is certain not to contain a blue token and therefore should not have been visited by the subject, i.e. between-errors + within-errors – double-errors.

SWM Double-errors

A record of the occasions where the subject has committed an error that can be categorised as both a 'within-error' and a 'between-error' . This is calculated for trials of four or more tokens only.

SWM Between-errors (6 boxes)

As 'between-errors' above but for 6 box problems only.

SWM Between-errors (8 boxes)

As above but for 8 box problems only.

SWM Strategy

Owen *et al.* (Neuropsychologia 1990: 28; 1021-1034) have suggested that an efficient strategy for completing this task is to follow a predetermined sequence by beginning with specific box and then, once a blue token has been found, to return to that box to start the new search sequence. An estimate of the use of this strategy is obtained by counting the number of times the subject begins a new search with the same box for 6- and 8-box problems. A high score represents poor use of this strategy and a low score equates to effective use. Thus, in the current study, the minimum strategy score is 1 for each stage (i.e.8) and the maximum is 1 for each search (i.e. 56).

3.4   OTHER PROCEDURES AND ASSESSMENTS

3.4.1   Well-being Visual Analogue Scales

The subject completed visual analogue scales (VAS) on the evening of the day before dose in Period 1 and thereafter, in each period, prior to dose administration, at ten minutes after the final dose increment, and at precisely three hours, eight hours and twelve hours after start of dose.

Each scale comprised a question, followed by a 10 cm line with an 'anchor' at either end, describing the extremes of possible answers. The questions and anchors were as follows:

How awake are you? (0 = very drowsy, 10 = fully alert)
How well do you feel? (0 = terrible, 10 = wonderful)
How would you describe your mood? (0 = terrible, 10 = wonderful)
Is your mouth dry? (0 = very dry, 10 = normal moisture)
How hungry are you? (0 = very hungry, 10 = not hungry)
Are you experiencing any unpleasant effects right now? (0 = very unpleasant effects,
                                                        10 = no unpleasant effects)

In addition the subject was asked to identify any unpleasant effects (such as "distant", "light-headed", "vague", "euphoric", "confused", "clumsy", "memory loss") and asked:

"Are you experiencing any other effects you would like to describe?
If yes, give details:_____"

If a condition was recorded which was considered to be an expected result of receiving cannabis then it was not recorded as an adverse event unless its intensity reached at least moderate (according to ICH GCP criteria, please see Section 3.4.5)

The Investigator added further comments about the status of the subject as appropriate.

3.4.2 Cardiac Monitoring and Measurement of Vital Signs

Cardiac monitoring was continuous from pre-dose until four hours post dose and was then discontinued providing clinical status was satisfactory. A print-out of the entire interval was made.

Blood pressure and pulse were recorded in the CRF pre-dose and at 5, 10, 15, 30 and 45 minutes and 1, 2, 3, 4, 6, 8 and 12 hours after the start of dose administration (before blood sampling).

3.4.3 Conjunctival Reddening

Conjunctival reddening was assessed prior to dose administration and at 15, 30 and 45 minutes, and 1, 2, 4, 8 and 12 hours after start of dose administration. The appropriate score was recorded as follows:

Table 1
Conjunctival reddening score

Description	Score
No reddening apparent	0
Slight reddening	1
Moderate reddening	2
Severe reddening	3

Comments could be added (e.g. 'affecting one eye only', 'associated itching').

3.4.4 Pharmacokinetics

Blood samples (approximately 5 ml) were taken via a cannula inserted in a suitable forearm vein, at the following times during each period:

Pre-dose and at 5, 10, 15, 30 and 45 minutes and 1, 2, 3, 4, 6, 8 and 12 hours after the start of administration.

3.4.5 Adverse Events

An adverse event was defined as any undesirable experience occurring to a subject during the course of the study, irrespective of the relationship to the test treatment.

Adverse events and concomitant medication were recorded throughout the study. Subjects were observed, asked non-leading questions concerning their well being and on occasions gave spontaneous reports. For each adverse event the Investigator recorded the date (and time if available) of onset and offset, the frequency (constant, intermittent, transient), the maximum intensity (mild, moderate, severe), whether treatment was given and the details of any treatment, and the outcome of the event, whether resolved or on-going. The Investigator also determined and recorded whether the event was serious and the degree of relationship to the test treatment (definite, probable, possible, not related).

The categories of adverse events were assessed according to the International Conference on Harmonisation Good Clinical Practice Guidelines (copy available on request).

CHAPTER 4   ANALYSIS AND STATISTICAL METHODS

4.1   DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The demographic data and baseline characteristics are tabulated and held on file.

4.2   CANTAB EFFICACY ANALYSIS

The data for PAL Stages Completed, PRM Number Correct and RVP Total False Alarms were not appropriate for analysis of variance (ANOVA) so these variables were not formally analysed but were summarised, tabulated and held on file.

For each of the other efficacy variables the differences between treatments were analysed using an ANOVA allowing for the effects of subject, period (as a continuous covariate) and treatment. A treatment by period interaction was tested for and removed from the model. Where the treatment effects were statistically significant then tests for all the pairwise comparisons were performed. Adjusted means from the ANOVA were presented with 95% confidence intervals. The residuals from the analysis were inspected to assess whether the parametric assumptions were reasonable.

The adjusted (or least-squares) means correct for subject and period to produce the marginal treatment means that would be expected for a balanced design with the other factors/covariates at their mean values.

For each of the other efficacy variables and each treatment the differences between time-points were analysed using an ANOVA allowing for the effects of subject and time-point. Where time-point was statistically significant, tests for all the pairwise comparisons were performed. The residuals from the analysis were inspected to assess whether the parametric assumptions were reasonable.

Results were considered to be statistically significant if the p-value was less than 0.05. In order to provide some protection to the overall type 1 error rate the pairwise tests were only performed where the overall effect was statistically significant. As this was an exploratory pilot study no adjustment was made to the type 1 error for the fact that there were several variables analysed at several time-points.

CHAPTER 5   RESULTS

The results are discussed in general terms below with means presented where appropriate and are further described by individual subject in Appendix A.

5.1   STATISTICAL OUTCOME OF CANTAB TESTING

5.1.1   Demographics, Baseline Characteristics and Dosage details

Demographic details are summarised in the table below:

Table 2
Summary of demographics (n = 6)

Subject no.	Age (yrs)	Weight (Kg)	Height (cms)	Body Mass Index	Smoking cigs/day	Alcohol Consumption
Male subjects						
01	35	82.0	184	24.2	< 6	< 22
02	42	76.5	172	25.9	Non-smoker	< 22
05	34	80.0	172	27.0	Non-smoker	< 22
Mean	37	79.5	176	25.7		
Female subjects						
03	38	64.3	175	21.0	< 6	< 15
04	30	60.4	166	21.9	< 6	< 15
06	43	69.1	161	26.7	Non-smoker	< 15
Mean	37	64.6	167.3*	23.2		

Each subject received all four treatments. Therefore it was not necessary to assess differences between demographics and baseline characteristics. Five subjects took the total dose in each period. Subject 03 took five of the possible eight increments with THC:CBD, 1:1 and six increments with High THC.

Table 3
Dosage per Kilogram of body weight

Subject no.	Weight (Kg)	Total dosage per Kg body weight (per increment) mg			
		THC:CBD,1:1		High THC	High CBD
		THC	CBD	THC	CBD
Male Subjects					
01	82.0	0.244 (0.030)	0.244 (0.030)	0.244 (0.030)	0.244 (0.030)
02	76.5	0.261 (0.033)	0.261 (0.033)	0.261 (0.033)	0.261 (0.033)
05	80.0	0.250 (0.031)	0.250 (0.031)	0.250 (0.031)	0.250 (0.031)
Female Subjects					
03	64.3	0.194 (0.039)	0.194 (0.039)	0.233 (0.039)	0.311 (0.039)
04	60.4	0.331 (0.041)	0.331 (0.041)	0.331 (0.041)	0.331 (0.041)
06	69.1	0.289 (0.036)	0.289 (0.036)	0.289 (0.036)	0.289 (0.036)

5.1.2 Efficacy Analysis

Inspection of the residuals showed that the assumptions for the analysis were reasonably upheld. Results which statistically significant are presented in bold text.

PAL Stages Completed

- There was no evidence of a treatment by period interaction for any of the time-points.
- There was no evidence of a period effect for any of the time-points.
- There was no evidence of a treatment effect for any of the time-points.
- There was no evidence of differences between time-points for any of the treatments.

PAL Total Trials – Adjusted

- There was no evidence of a treatment by period interaction for any of the time-points.
- There was no evidence of a period effect for any of the time-points.
- There was no evidence of a treatment effect for any of the time-points.
- There was no evidence of differences between time-points for any of the treatments.

RTI Simple Reaction Time

- There was no evidence of a treatment by period interaction for any of the time-points.
- There was no evidence of a period effect for any of the time-points.
- There was no evidence of a treatment effect for any of the time-points.
- There was no evidence of differences between time-points for any of the treatments.

RTI Five-Choice Reaction Time

- There was no evidence of a treatment by period interaction for any of the time-points.
- There was no evidence of a period effect for any of the time-points.
- There was no evidence of a treatment effect for any of the time-points.
- There was no evidence of differences between time-points for any of the treatments.

RVP Total Hits

- There was no evidence of a treatment by period interaction for any of the time-points.
- There was no evidence of a period effect for any of the time-points.
- There was no evidence of a treatment effect for any of the time-points.
- There was no evidence of differences between time-points for any of the treatments.

RVP Mean Latency

- There was no evidence of a treatment by period interaction for any of the time-points.
- There was no evidence of a period effect for any of the time-points.
- There was no evidence of a treatment effect for any of the time-points.
- There was no evidence of differences between time-points for any of the treatments.

SSP Span Length

- There was no evidence of a treatment by period interaction for any of the time-points.
- There was no evidence of a period effect for any of the time-points.
- There was no evidence of a treatment effect for any of the time-points.
- There was no evidence of differences between time-points for any of the treatments.

SWM Between-errors

- There was no evidence of a treatment by period interaction for any of the time-points. **There was a statistically significant (p=0.012) period effect for the 10 minutes time-point.**
- **There was a statistically significant (p=0.023) treatment effect for the 3 hours time-point with treatments THC:CBD, 1:1 and High THC both having statistically significantly larger values than placebo.**
- There was no evidence of differences between time-points for any of the treatments.

SWM Between-errors (6 Boxes)

- **There was a statistically significant (p=0.005) treatment by period interaction for the 8 hour time-point, which means that the effect of treatment is dependent on which treatment period it was given.**
- **There was a statistically significant (p=0.050) period effect for the 10 minutes time-point.**
- There was no evidence of a treatment effect for any of the time-points.
- There was no evidence of differences between time-points for any of the treatments.

SWM Between-errors (8 Boxes)

- **There was a statistically significant (p=0.026) treatment by period interaction for the 3 hour time-point, which means that the effect of treatment is dependent on which treatment period it was given.**
- There was no evidence of a period effect for any of the time-points.
- There was no evidence of a treatment effect for any of the time-points.
- There was no evidence of differences between time-points for any of the treatments.

SWM Within-errors

- There was no evidence of a treatment by period interaction for any of the time-points.
- There was no evidence of a period effect for any of the time-points.
- There was no evidence of a treatment effect for any of the time-points.
- There was no evidence of differences between time-points for any of the treatments.

SWM Strategy

- **There was a statistically significant (p=0.009) treatment by period interaction for the 3 hour time-point, which means that the effect of treatment is dependent on which treatment period it was given.**
- There was no evidence of a period effect for any of the time-points.
- There was no evidence of a treatment effect for any of the time-points.
- There was no evidence of differences between time-points for any of the treatments.

SWM Total Errors

- There was no evidence of a treatment by period interaction for any of the time-points.
- **There was a statistically significant (p=0.008) period effect for the 10 minutes time-point.**
- **There was a statistically significant (p=0.023) treatment effect for the 3 hours time-point with treatments THC:CBD, 1:1 and High THC both having statistically significantly larger values than placebo.**
- There was no evidence of differences between time-points for any of the treatments.

PRM Number Correct – Delayed

- There was no evidence of a treatment by period interaction for any of the time-points.
- There was no evidence of a period effect for any of the time-points.
- There was no evidence of a treatment effect for any of the time-points.
- **There was a statistically significant (p=0.020) difference between time-points for treatment THC:CBD, 1:1 with the 8 hour time-point being statistically significantly smaller than the other 2 time-points.**

5.1.3   Conclusions on CANTAB Statistical Outcome

Statistically significant effects were few. These findings should however be viewed with some caution as with the small study population (six subjects) in this pilot study there was insufficient power to detect small differences.

The only statistically significant treatment effects were at three hours for SWM between-errors and SWM total-errors (THC:CBD versus Placebo, and Placebo versus High THC) but these variables were very highly correlated.

The only statistically significant period effects were at ten minutes after final dose increment and affected SWM between-errors, between-errors (6 boxes) and total-errors. There was insufficient evidence for any other period effects.

Treatment-by-period interactions were statistically significant for SWM: at eight hours after dose for between-errors (6 Boxes), and at three hours for between-errors (8 boxes) and strategy.

There was a single statistically significant time-point effect with THC:CBD, 1:1 affecting PRM Number Correct – Delayed (10 minutes versus eight hours and three hours versus eight hours).

The study design entailed all subjects taking treatment THC:CBD, 1:1 in the first period. Thus 'period' had to be fitted as a linear covariate. This was not an ideal way to fit the model but was necessary to separate the period results from the treatment results in Period 1. Inspection of the residuals did not suggest that fitting 'period' as a linear covariate was implausible.

Other cognitive trends apparent on analysis

Due to the small sample size in this study, it is interesting to look at some of the general trends shown by the results and analysis. Tables summarising descriptive statistics for key measures for each treatment and time-point, and tables showing the p-values by endpoint and time-point for all subjects are held on file.

These tables show a trend towards a treatment effect for five choice reaction time at ten minutes. Consideration of the adjusted means for each treatment shows that the subjects took longer to respond on this reaction time task following administration of either THC:CBD, 1;1 (372.2 versus 349.0 minutes) or High THC (395.5 versus 349.0 minutes) when compared respectively to placebo. On rapid visual Information processing (RVP), a sustained attention and vigilance task, the subjects had a tendency to make fewer hits with either High CBD (20.8) or THC:CBD, 1:1 (20.4) when compared separately to placebo (23.4).

There appears to be a tendency to impaired performance on the spatial span test, a short-term working memory task, when High THC (sequence of 5 boxes remembered) is compared with placebo (sequence of 6.4 boxes remembered) at the 10 minutes time-point.

5.2 OTHER PHARMACODYNAMIC RESULTS

5.2.1 Timing of Subjective Awareness of Effect

The onset of effect, as evinced by subjective VAS, unsolicited subjective reports and objective reports from the Investigator, were as follows:

Table 4
Subjective first effects

| CBME | n | First Effects Apparent (time after start of dose in minutes) | | |
		Mean	Median	Range
THC:CBD,1:1	6	66	85	26 to 85
High THC	6	42	45	23 to 58
High CBD*	4	30	23-35	18 to 85
Placebo**	3	52	50	45 to ~60

*Two subjects not aware of any effect **Three subjects not aware of any effects*

5.2.2 Well-being Visual Analogue Scales

The subjects addressed visual analogue scales (VAS) prior to dose, at ten minutes after the final dose increment and at three, eight and twelve hours after start of dose. Due to the low subject population the results were not submitted to statistical analysis. The results are summarised by variable in this section and by subject in Chapter 6. There was marked inter-subject variability throughout but the mean scores are shown graphically below for two variables for which trends were apparent.

Alertness

Baseline scores were variable. There was a clear, though not invariable, tendency for the lowest scores (decreased alertness) to be recorded at three hours after dose, usually followed by a gradual increase in score. This tendency was present, but less marked, with placebo, and was marginally less marked with High CBD than with the other two active CBMEs.
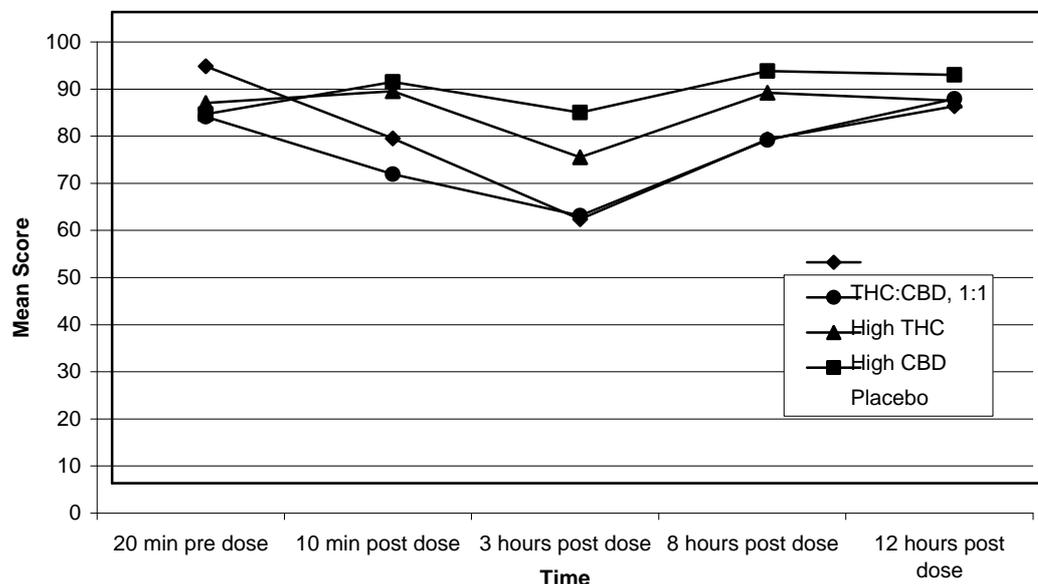
Figure 1
Visual Analogue Scales: Mean Alertness

Well-being

Changes from baseline (usually high scores) were moderate overall. Subjects 05 and 06 tended to score lower than the other subjects throughout. Scores below individual baseline, indicating a decreased degree of well-being, were recorded at any time after start of dose but were usually moderate and did not appear to indicate a general tendency.

Mood

Subjects 01 and 02 scored close to 100 throughout, indicating a 'wonderful' mood. The other subjects, particularly 05 and 06, were somewhat lower. There was a very moderate tendency with THC:CBD, 1:1 and High THC for lower scores at various times after dose with a degree of recovery (not universal) by 12 hours. No clear pattern of change was apparent with either High CBD or placebo.

Oral Moisture

Marked decreases in scores (from variable baselines), indicating an increase in mouth dryness, were recorded after dosing with THC:CBD, 1:1 and High THC. Similar scoring patterns over time were seen with High CBD and placebo but the degree of score change was less with High CBD than the other two active CBMEs and marginal with placebo.

Figure 2
Visual Analogue Scales: Mean Mouth Dryness

Hunger

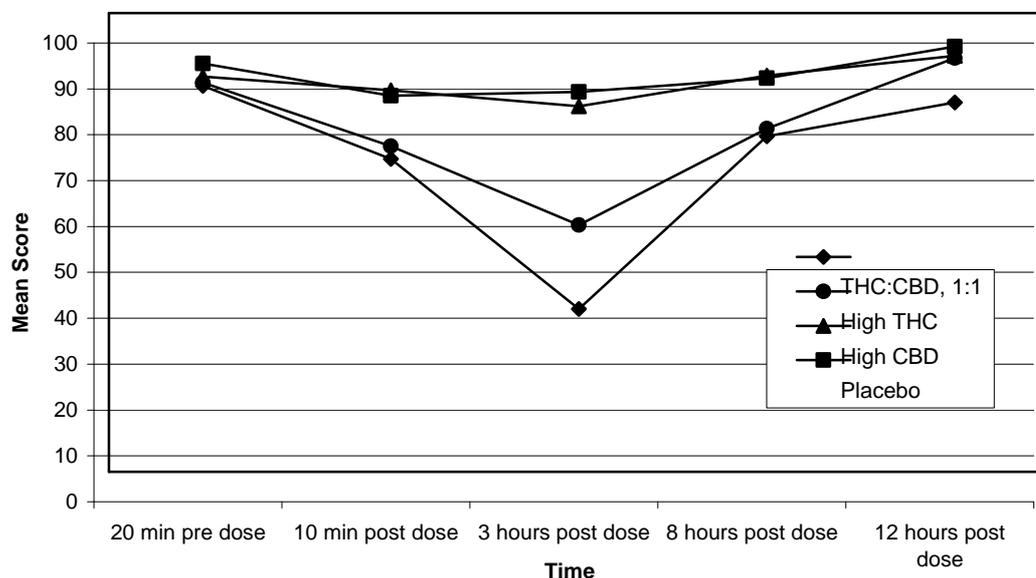The baseline scores were very variable. There was a clear tendency with all treatments including placebo for hunger to increase at three hours after dose. This was prior to lunch, given at four hours, after which scores usually increased markedly.

Unpleasant Effects

Baseline scores were usually high, often 99 to 100, indicating no unpleasant effects. There were no overall marked changes in scores. Isolated changes were at various times after dose.

5.2.3   Conjunctival Reddening

It is recognised that conjunctival reddening is a side effect of cannabis administration and increase in reddening was indeed noted during the treatment periods. However the use of this measure as an indication of the onset, duration and degree of effect of the medication was prejudiced by the fact that on five occasions (Subject 05 three occasions, Subjects 01 and 02, single occasion) slight reddening was present before dosing, and also that four of the six subjects displayed reddening after treatment with placebo, albeit mainly transiently.

Most commonly however the conjunctiva was noted to be slightly red at between 15 and 30 minutes after start of dose and for the redness to persist or increase until at least four hours, which was broadly consistent with the appearance of the psychoactive effects. Subject 05 consistently received the highest scores and it seems a degree of reddening was normal to this subject for whom 'severe' reddening of brief duration was noted during treatment with THC:CBD, 1:1 and with High THC. Subject 03 was the only other subject to receive a score greater than 'slight'. This occurred at two hours after start of dose with THC:CBD, 1:1 but by the following assessment at four hours was again only slight.

5.3 SAFETY RESULTS

5.3.1 Adverse Events

There were no serious adverse events and no adverse events which led to withdrawal.

Full details of the adverse events (dates and times of onset and offset, time of occurrence in relation to time of start of dose, frequency, maximum intensity, treatment required, outcome, relationship to Test Article and whether the event was serious) are held on file by GW Pharmaceuticals Ltd. All six subjects reported at least one adverse event to an overall total of 62. Four of these (three subjects) persisted into more than one period and were therefore recorded more than once.

The table immediately below shows the number of adverse events by relationship to treatment at their first occurrence only.

Table 5
No of adverse events (no of subjects)

CBME	Relationship to Test Article				Total
	Definite	Probable	Possible	Not related	
THC:CBD,1:1	2 (2)	6(2)	1(1)	3(2)	12(4)
High THC	0	4(3)	4(2)	3(1)	11(4)
High CBD	0	1(1)	3(2)	1(1)	5(3)
Placebo	0	1(1)	0	2(1)	3(1)
Total	2(2)	12(4)	8(4)	9(3)	31(6)

The table overleaf lists the adverse events by description.

Table 6
No of adverse events by relationship to treatment at first occurrence

Adverse event	THC;CBD,1:1	High THC	High CBD	Placebo
Burn mark left hand			Not related	
Conjunctival reddening	Definite			
Conjunctival reddening	Definite			
Disturbed sleep pattern			Possible	
Extreme hunger	Probable			
Headache	Not related			
Headache				Not related
Hot flush		Possible		
Hot flush		Possible		
Hot flush		Possible		
Hypotension	Probable			
Increased stool frequency	Possible			
Intermittent pyrexia		Possible		
Low mood			Possible	
Oedema both hands				Not related
Pallor	Probable			
Pallor		Probable		
Runny nose		Not related		
Menopausal symptoms	Not related			
Sore throat		Not related		
Stomach cramps			Possible	
Sweating	Probable			
Tachycardia	Probable			
Tachycardia		Probable		
Tachycardia		Probable		
Toothache	Not related			
Vivid dreams	Probable			
Vivid dreams			Probable	
Vivid weird dreams		Probable		
Vivid unusual dreams				Probable
Yellow sputum		Not related		
Summary				
Definite	2	0	0	0
Probable	6	4	1	1
Possible	1	4	3	0
Not related	3	3	1	2
Total:	12	11	5	3

The great majority (>86%) of adverse events which were to any degree related to treatment were of brief (less than 24 hours) or transient duration and none of these required medication. All except one were classified as of mild or moderate intensity. The one 'severe' event was conjunctival reddening (Subject 05, definitely related to THC:CBD, 1:1) which resolved without intervention.

The most common adverse event was sleep disturbance (six events) usually described as vivid dreams. This occurred with all treatments and was either possibly or probably related.

Continuous cardiac monitoring showed brief intermittent episodes of mild tachycardia during or following dose administration, an effect reported in the literature. On three occasions the heart

rate was noted to have reached between 112 and 120 beats per minute and these episodes were recorded as adverse events probably related to treatment. One occurred with THC:CBD,1:1, and two with High THC. The former (Subject 02, male) was associated with an episode of hypotension which occurred at ten minutes after the final dose increment as the subject moved from a semi-prone position to sit on the edge of the bed in order to undertake the cognitive assessments. The hypotension was therefore considered to have a postural element and was concurrent with pallor and sweating (also recorded as adverse events).

Conjunctival reddening is also a known effect of cannabis administration and was assessed and scored at times relative to dosing and recorded as an adverse event only if it reached moderate intensity (two occasions, both with High THC).

There were two instances of pallor (probably related to THC:CBD, 1:1 and High THC), one of sweating (probably related to THC:CBD, 1:1) and three instances of hot flushes of possible relationship to treatment. However the latter were all for Subject 06, who was believed to be menopausal.

Hunger is anecdotally reported to be common following recreational use of cannabis and occurrence of this was monitored using visual analogue scales. On one occasion hunger was described as 'extreme' and recorded as a probably related adverse event. However it occurred in the early morning prior to dose administration. Single subjects reported abdominal cramps and increased stool frequency (brief duration).

Nine events of no relationship to treatment were recorded such as menopausal symptoms, headaches, and symptoms related to mild infections.

Four events persisted through more than one period. Two were of no relationship to treatment and comprised menopausal symptoms and toothache. The remaining two were of possible relationship (assessed for the Test Article in the period in which they first appeared, High CBD) and were disturbed sleep and 'low mood', both for Subject 01. No intervention was required.

The only concomitant medication taken during the study was by Subject 05 (male), who took two packets of Lemsip daily for four days for an intermittent high temperature and by Subject 06 who on two occasions took Nurofen 400 mg for headache.

5.3.2 Cardiac Monitoring and Measurement of Vital Signs During Periods

The mean (standard deviation) blood pressure and pulse rates at each time point for each treatment are held on file. The change from baseline in mean heart rates for the first four hours after start of dose are presented in the following figure. Please note the heart rate was recorded for the first four hours from the cardiac monitor, thereafter the radial pulse rate, taken manually, was recorded.
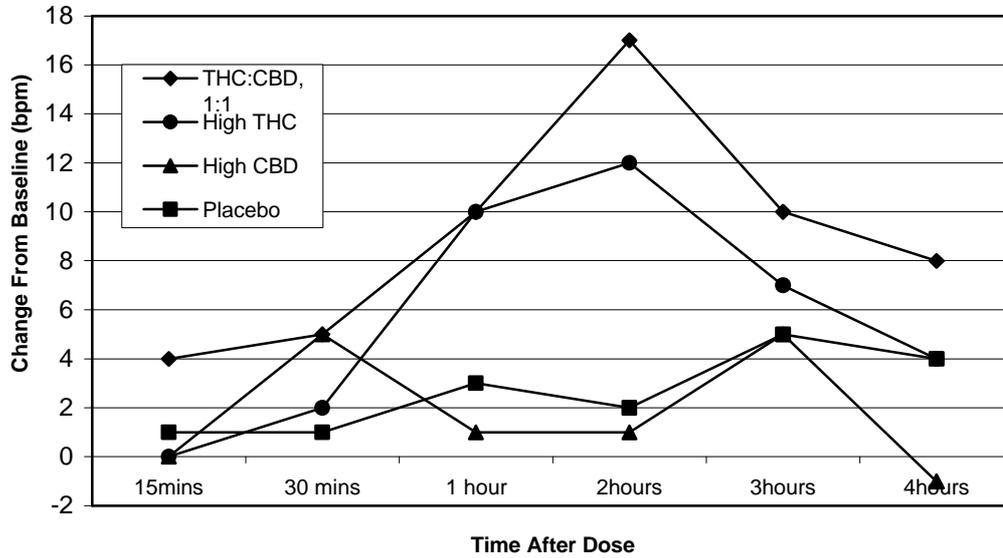

Figure 3
Mean Heart Rate: Change from Baseline

The mean diastolic blood pressure was between 66 and 83 mmHg throughout, but only infrequently above 75 mmHg for all treatments except THC:CBD, 1:1, with which it was between 82±09 and 83±10 mmHg from five minutes after start of dose until 45 minutes, having been 76 mmHg pre dose. The concomitant systolic pressure was between 121±12 and 125± 14 mmHg and therefore well within normal range. Normotensive diastolic pressure range is usually considered to be 60 to 85 mmHg, so the recorded mean is towards the upper limit of the norm. However this was the first period for all subjects who may therefore have experienced more stress than in later periods when the procedures, surroundings and staff were more familiar.

The normal pulse rate range is usually considered to be 60 to 80 beats per minute but in a relatively young, healthy subject who exercises strenuously on a regular basis the normal resting pulse rate may be substantially lower. Mean rates were between 56 and 73 throughout, well within accepted range. The highest means were recorded in the first period, but no apparent trends of clinical significance were observed.

5.3.3 Comparison of Clinical Results at Pre and Post Study Screening

Clinical Laboratory Evaluation

Values outside the normal range for the testing laboratory were noted but the majority of these were marginal and not clinically significant in the judgment of the Investigator.

Prior to the study a gamma GT result of 71 IU/L (normal maximum for females: 40 IU/L) was noted for Subject 06. A repeat sample showed a concentration of 67 IU/L which was considered acceptable for study entry.
There were no clinically significant changes noted after the study.

Vital Signs, Physical Examination and Electrocardiography

The individual and mean (standard deviation) measurements of pulse rate, blood pressure and weight are shown in the table below:

Table 7
Vital signs and weight before and after the study

Subject No.	Pulse rate (beats/ min)		Blood pressure (mm/Hg) systolic		diastolic		(Arm)	Weight (Kg)	
	Pre-	Post-	Pre-	Post-	Pre-	Post-		Pre-	Post-
01	51	54	138	133	76	71	(Left)	82.0	83.0
02	68	57	129	120	79	72	(Left)	76.5	81.9
03	74	76	115	108	65	65	(Right)	64.3	64.5
04	67	81	113	122	67	71	(Left)	60.4	64.0
05	59	68	139	145	84	93	(Left)	80.0	80.0
06	87	68	115	123	69	81	(Left)	69.1	70.0
Mean	68	67	125	125	73	76	-	72.05	73.90
SD	12.39	10.46	12.04	12.58	7.50	9.99	-	8.79	8.78

An increased blood pressure was noted post study for Subject 05 (male). Otherwise there were no changes in mean or individual blood pressure or pulse rate which gave rise to clinical concern.

An increase in weight was noted for five of the six subjects after the study. This may be partly accounted for by more clothes being worn due to colder weather but it was also noted that a different set of weighing scales was used post-study for some subjects. The Investigator did not consider these changes to be clinically significant.

No abnormalities were observed on physical examination before or after the study.

All post study ECGs were normal or normal variants and there were no marked changes from the pre study recordings.

Hospital Anxiety and Depression Score (HAD)

In order to exclude any subject who might suffer a clinically significant degree of anxiety or depression (with particular reference to undertaking the cognitive assessments) the HAD assessment was undertaken before and after the study. The resulting scores are shown below:

Table 8
HAD scores before and after the study

Subject no	Score			
	Anxiety		Depression	
	Pre	Post	Pre	Post
01	5	7	3	5
02	2	6	1	1
03	3	3	1	6
04	2	7	1	4
05	8	8	1	5
06	4	2	0	0
Mean*	4.0	5.5	1.2	3.5

*Rounded to one decimal place

Increased scores were noted for both parameters after the study in comparison to the pre-study results. However all individual scores were under 10, the level suggesting clinical significance.

CHAPTER 6   INTERPRETATION OF RESULTS

This probe study in six healthy volunteer subjects showed clear evidence of the presence of THC following sublingual administration of CBME. Psychoactive effects and other known effects of cannabis administration were observed, such as conjunctival reddening and intermittent tachycardia, which was however of brief duration. The former is not of clinical concern and indeed can be a helpful indication of dose effect. The latter will be of concern in the clinical setting for those patients with significant cardiac conditions. These will be excluded from trials, at least until a significant corpus of safety data accumulates.

It was understood that the probability of finding statistically significant changes was small given the size of the subject population. The study was rather aimed at identifying areas for further, more focussed assessment.

All results should be viewed in the light of the doses given. It was the intention to give a sufficient amount in this study to render the subjects 'high', providing this was tolerable to them. The dose was given in increments (which could be discontinued at any time if effects were unacceptable) because, as has been stated, there were difficulties in estimating the dose of CBME required to achieve approximation to a recreational 'high' for the following reasons:

- there is little if any published data concerning sub-lingual administration
- the cannabinoid content, quality and age of illegally obtained recreational cannabis is subject to wide variability, and is therefore impossible to replicate.
- there is individual variability in response

The third point was illustrated in the study by the fact that the subjects who appeared to feel the psychoactive effects most strongly were not those for whom the dose in relation to body weight was the highest. However five of the six subjects reported feeling 'high' or 'very high' with the two active CBME which contained a high ratio of THC. The subjects may thus be considered in broad terms to have had the equivalent to a moderate recreational dose, which is expected to be markedly higher than the medicinal dose required for the majority of patients.

Judging by the subjective reports the first onset of effects was from between approximately twenty minutes to one and a half hours after start of dose. On occasions other signs or the appearance of the subject suggested that the medication was active before the subject was aware. Because the disappearance of the effects was gradual the time of offset can only be given in approximate terms but psychoactive effects were not usually apparent after four hours and any later subjective comments were mainly of tiredness, not of course necessarily related to the test treatment.

All active treatments showed more effect than placebo and the High CBD ratio produced less adverse events, as expected, than the ratios with greater THC content. No adverse events gave rise to on-going clinical concern.

Overall the effect on cognitive function did not appear marked.

The type of cognitive tasks used in the study are designed to provide laboratory measures of particular cognitive functions in the absence of the many uncontrolled variables that one would encounter in the outside world. They are relevant to our understanding of how cannabis might affect everyday tasks. For example, if consistent problems in working memory were found, deficits in everyday tasks that involve that kind of memory function might be expected.

However, there is no precise, predictive relationship between results 'in the laboratory' and what happens in the real world. This is particularly true when the results are obtained from a small, highly-selected group of volunteers, within a highly controlled environment, and with arbitrary timing of the test sessions, as is the case in this study. The applications of results to actual tasks given below should therefore be viewed as speculative, and as of interest in identifying areas of concern rather than stating a clear relationship.

The only statistically significant treatment effect was a worsening of performance on the spatial working memory test (SWM). 'Between-search errors' were increased compared to placebo at three hours after dose with both THC:CBD, 1:1 and High THC. This test taps an important aspect of executive function, which is the ability to organise cognitive activity behaviour effectively and relates to problem–solving ability, the induction of strategy in novel situations and, for example, the overriding of habitual but inappropriate action. Specifically, Spatial Working Memory assesses the ability to organize information stored in short term memory in order to facilitate a more efficient search for visual information ('targets in the display'). However, there was no deficiency in spatial span (SSP), except a slight tendency to impaired performance with High THC at ten minutes after dose. Spatial span is one component function necessary for the performance of spatial working memory. It comprises the ability to keep a record of spatial information as required, for example, when an air traffic controller must keep mental track of the recent positions of planes on a visual display.

There was no apparent effect on either paired associate learning (PAL), an important measure of associative learning and retrieval from longer-term memory, or in pattern recognition memory (PRM), another important measure of visual memory which contrasts to PAL. These tests are relevant to learning, remembering and following verbal or written procedures and instructions, or physical lay-out and are thus basic to a wide range of tasks.

Mild trends in impairment were apparent in results for the reaction time and vigilance tasks. Reaction time is a simple measure of the speed of a given motor response to a given visual stimuli. For the more complex of the two reaction time tests, some evidence was noted of slower reaction at ten minutes after final dose increment (but not later) for both of the formulations with high THC content (THC:CBD, 1:1 and High THC). This function has an obvious relevance to any situation which requires fast and accurate responses to targets as they are presented. Clearly such situations include driving or operating machinery and equipment.

Rapid visual information processing (RVP) tests the ability to sustain attention across time (it also includes a limited memory component) during a repetitive or boring task, such as listening to a lecture, watching for aircraft on a radar screen or watching a conveyor belt for faulty units. It might also apply to long-distance motorway driving. There was a tendency to lower performance (fewer 'hits') with both the CBME formulations which have high CBD content (THC:CBD, 1:1, and High CBD), but not with CBME High THC. This is of interest in the light of anecdotal reports of recreational cannabis aiding the concentration or ability to focus in what would usually be regarded as a boring task. Recreational cannabis will usually have high THC content and of course much larger doses may be taken than in this study.

The results overall indicated that cannabis with a high THC content, which would include most recreational supply, had some effect on complex cognitive ability and reaction time, while cannabis with a high CBD content, which may in the future prove efficacious in certain medicinal use but is not welcome in recreational use, may have had a limited effect on vigilance. At the doses given in this study the impairments were minor, but unregulated recreational use is not of course limited to a dosing regime. The observed tendencies may be mitigated by the increased awareness of impairment experienced with cannabis which, in the driving seat for example, tends to lead to caution and exertion of compensatory effort (Ward and Dye, 1999).

ACKNOWLEDGEMENTS

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APPENDIX A   INDIVIDUAL SUBJECT DESCRIPTION AND ANALYSIS

In addition to the full statistical analysis presented, the small subject size enables examination of the performance of the individual on certain key measures. In the next section, for each subject, baseline details are given, key patterns of CANTAB performance are reported (on all but the reaction time task, where latency measures were examined for the group as a whole), and other effects including safety variables are summarised. Some reference is made to the differences in performance in the CANTAB tests between the different treatment conditions and time-points. However, the analysis should be treated with caution since it is difficult to determine the significance of a change without examining the performance of the group as a whole. In addition, looking at individual performance takes no account of the order in which treatments were administered, whereas the statistical model fitted has factored this into the model.

A.1   SUBJECT 01

A.1.1   Baseline Findings

Subject 01 was a 35 year old male weighing 82 Kg and 184 cm tall. No medical history of note was recorded. He had commenced using cannabis at about age 18 and current use was approximately once a month.

The maximum dose was taken in each period and the dosage per Kg of body weight was 0.244 mg (0.030 mg per increment).

A.1.2   CANTAB Results

Spatial Working Memory

During treatment with THC:CBD, 1:1, in Period 1, the subject made 33 and 41 between-errors, at 10 minutes and 3 hours respectively, compared with only 10 between-errors at 8 hours. The number of between-errors made with other treatments was lower, particularly with High THC, although this was in treatment Period 4 and a learning effect was probably operating. The strategy score remained relatively constant throughout all treatments.

Paired Associative Learning

For all treatments, the subject reached the end of the test, completing all stages successfully. The subject made the most number of errors (23) during treatment with High CBD at 8 hours.

Pattern Recognition Memory (immediate and delayed)

For all treatments, the subject was performing at near ceiling in the immediate recognition phase. In the delayed recognition test, the subject made an increased number of errors at 10 minutes and 8 hours during treatment with THC:CBD, 1:1 and at three hours after treatment with High CBD.

Spatial Span

Overall the span length range was 5 to 8 boxes. During treatment with THC:CBD,1:1, the subject's performance decreased from a span length of 8 boxes at 10 minutes to 5 boxes at 3 hours. It then improved to a span length of 7 when measured at 8 hours. There were no marked changes following administration of placebo or High CBD. However, with High THC, the span length was 5 boxes during the 10 minute time-point, improving to 8 boxes thereafter.

Rapid Visual Information Processing

The range for the total number of hits made across all treatments was 18 to 27, although the lowest number of hits overall was made during the first treatment period with treatment THC:CBD, 1:1. Performance during the subsequent periods did not vary markedly between time-points and treatments.

A.1.3   Other Effects Including Safety

Times of effect

Table 9
Subject 01 Onset of effects by treatment

Variable	THC:CBD, 1:1	High THC	High CBD	Placebo
First effects apparent	40 mins	23 mins	23 mins	-
Peak or plateau	~ 3 hours	2 hours 45 mins	<2 hours	-
Offset of effects if apparent	> 3 hours	> 4 hours	-	-
Description of effects, if any	"Mellow, chilled out, very high"	Relaxed	Relaxed. "slowed up" at 2 hours Drowsy at >3 hours	Nil

Visual Analogue Scales (VAS) (maximum score= 100):alertness

Having been 'fully alert' pre-dose (except with High THC, score 77) there was a decrease in scores, to a low of 66 at three hours with THC:CBD, 1:1, to 47 at eight hours with High THC and to 33 at three hours with High CBD, followed by an approximate return to full alertness at twelve hours except with High CBD (twelve hours: score 75). The effect was slightest with placebo (nadir at three hours: 80).

VAS: well-being

The scores remained at 99 or 100 indicating a feeling of 'wonderful' well being except for a fall to 93 with THC:CBD, 1:1, and a fall to 87 with High CBD, both at three hours.

VAS: mood

The pre-dose score was 99 or 100 indicating that mood was, or was close to 'wonderful'. The most marked decreases from this were to 78 with High CBD and to 93 with THC:CBD, 1;1 both at three hours. With placebo there were falls only at eight hours (98) and twelve hours (99). The lowest score with High THC was 98 at three hours and with High CBD was 95 at eight hours.

VAS:oral moisture

There was marked mouth dryness with THC:CBD, 1:1 with scores falling from the pre-dose 100 (normal moisture) to 46, 43 and 72 at ten minutes, three and eight hours respectively, and a return to 100 at twelve hours. The pattern of dryness after dosing was repeated with the other active treatments but not to same degree (nadir with High THC, 77, with High CBD, 83, both at three hours). Only a minor effect (score of 98) was recorded for placebo.

VAS: hunger

The pattern of recorded degree of hunger was erratic. The pre-dose scores indicated some hunger (range from 43 with THC:CBD, 1:1, to 77 with High THC, 100 would equal no hunger) after which there were moderate increases in score, indicating less hunger, followed by a decrease, showing more hunger at three hours with all active treatments, and at eight hours with placebo. Scores thereafter increased (twelve hours: 99 or 100) as expected following the main meal at nine hours.

VAS: unpleasant effects

The majority of scores were 99 or 100 indicating an absence of unpleasant effects. However a score of 80 was recorded at ten minutes after dosing with THC:CBD, 1:1 and the accompanying comment from the subject was "mellow, chilled out". Scores of 96 and 98 were recorded at ten minutes and three hours with High CBD, and a comment marked as given at two hours read "slowed up".

Conjunctival Reddening

Mild conjunctival reddening was noted with all treatments including placebo from 15 or 30 minutes after start of dose until after four hours but with High THC was present prior to dose and became severe at two and one half hours (see 'related adverse events').

Vital signs

Pre study	Blood pressure	138/76	mmHg	Pulse rate:	51	beats per minute
Post study	Blood pressure	133/71	mmHg	Pulse rate:	54	beats per minute

During treatment with THC:CBD, 1:1 in Period 1, the diastolic blood pressure was between 89 mmHg (at one hour) rising to 108 mmHg (at three hours) from the interval before dose to at least four hours after, and thus somewhat higher than the expected range. The systolic pressure for this interval was between 157 (three hours) and 132 mmHg (four hours) and the pulse rate (CRF record) ranged from 47 to 56 beats per minute (cardiac monitor showed intermittent rates above 70 bpm). Although relatively low, these are all acceptable results for a resting healthy young male. In no other period did the diastolic blood pressure for this subject rise above 90 mmHg except transiently at five minutes after start of dose with High CBD (93 bpm). The pulse rate (CRF record and cardiac print-out) seldom rose above 50 beats per minute, except from before dose until plus 45 minutes with THC:CBD, 1:1, when the range was 91 to 94 bpm.

Related Adverse Events

With THC:CBD, 1:1 this subject had severe conjunctival reddening from about two and one half hours after dose for one hour, definitely related to treatment. He also reported disturbed sleep pattern and 'low mood' starting two days after dosing with High CBD (Period 2), both of which persisted throughout the rest of the study. These were considered possibly related to treatment.

A.2   SUBJECT 02

A.2.1   Baseline Findings

Subject 02 was a 42 year old male weighing 76.5 Kg and 172 cm tall. No medical history of note was recorded. He had used cannabis only once, when aged 27.

The maximum dose was taken in each period and the dosage per Kg of body weight was 0.261 mg (0.033 mg per increment).

A.2.2   CANTAB Results

Spatial Working Memory

During treatment with THC:CBD 1:1, in Period 1, the subject made 73 between-errors at 10 minutes compared with 58 at three hours. However, a similar pattern of impaired performance at ten minutes compared to three hours can be observed with all other treatments, suggesting a learning effect operating on performance across that day. The strategy score remained relatively constant throughout all treatments.

Paired Associative Learning

The subject completed all stages of the test successfully during treatment with High THC and THC:CBD, 1:1. However, in the placebo and High CBD conditions, the subject reached the penultimate stage at both the ten minute and eight hour time-points. The range of errors made across all treatments was 5 to 52, and the subject made the most number of errors (52) during treatment with High CBD at eight hours.

Pattern Recognition Memory (immediate and delayed)

For all treatments, the subject was performing at near ceiling in the immediate recognition phase, scoring in the range 8 to 12. In the delayed recognition test, there was no consistent pattern of impairment when compared with performance in the placebo condition.

Spatial Span

Across all treatments, the span length range was 3 to 4 boxes, the subject attaining a span of 3 boxes on most test occasions. Thus, no pattern of impairment could be detected due to a floor effect.

Rapid Visual Information Processing

The range for the total number of hits made across all treatments was 9 to 19, although the lowest number of hits overall was made during the first treatment period with treatment THC:CBD, 1:1, at eight hours (9 hits) followed by High CBD (11 hits) and placebo (11 hits) both at ten minutes after end of dose.

A.2.3 Other Effects Including Safety

Table 10
Subject 02: onset of effects by treatment

Variable	THC:CBD, 1:1	High THC	High CBD	Placebo
First effects apparent	35 mins	<50 mins	Not apparent	-
Peak or plateau	~2hours 10	-	-	~1 hour
Offset of effects if apparent	>3½ hours	Effects decreasing but still apparent at ~3hours	-	-
Description of effects, if any	"hot inside" sweating, dizzy, unsteady. "high" Hypotensive episode	Pale, dizzy, tachycardic	nil	relaxed

Visual Analogue Scales (VAS)

(There was some doubt as to whether this subject fully understood the method of VAS scoring).

VAS:alertness

A score of 100, 'fully alert' was recorded at all time points except at pre-dose with High THC (score 99).

VAS: well-being, mood, oral moisture

Scores of 100 were recorded throughout, indicating wonderful well-being and mood, and normal moisture in the mouth except a score of zero at three hours with THC:CBD, 1:1 indicating a very dry mouth.

VAS: hunger

Scores of 99 or 100 were recorded for the majority of time points indicating no or very little hunger. There was a fall to 44 at eight hours with High CBD and to 54 and 63 at three and eight hours respectively with placebo.

VAS: unpleasant Effects

The scores were 100 throughout. However, comments regarding unpleasant effects were made, although not always at the precise times of the VAS records. Thus with THC:CBD, 1:1, the subject reported feeling "hot inside, sweaty and dizzy" at ten minutes after final dose increment, at which time he was observed to be hypotensive. With High THC the subject reported feeling light-headed from about 50 minutes after start of dose until at least three hours and with placebo reported feeling relaxed at about one hour after start of dose.

Conjunctival Reddening

With all treatments mild reddening was present from 30 or 45 minutes after start of dose until after four hours (active CBMEs) or eight hours (placebo).

Vital signs

Pre study	Blood pressure	129/79	mmHg	Pulse rate:	68	beats per minute
Post study	Blood pressure	120/72	mmHg	Pulse rate:	57	beats per minute

This subject experienced a hypotensive incident in Period 1 during treatment with THC:CBD, 1:1 (cf. 'unpleasant effects'). This occurred at ten minutes after the final dose increment when the subject assumed a more upright (but still sitting position) in readiness to undertake the cognitive assessment battery of tests. The subject had been aware of feeling effects from the medication for 45 minutes at this time.

There were no other such incidents recorded throughout the study and diastolic pressure remained between 67 and 85 mmHg except for a rise to 92 mmHg (systolic 102 mmHg) at three hours after start of dose (when effects would be considered to be near peak) with High THC. The pulse rate at this time (CRF record) was 83 bpm but at one hour previously was 102 bpm, substantially higher than the norm. There were no other changes of note for this subject except a pulse rate of 94 bpm recorded at six hours after dose in Period 1, THC:CBD, 1:1. However at this time the subjects were not confined to bed and the change in rate was not necessarily related to dosing.

Related Adverse Events

The incident and associated effects discussed in the above sub-section were recorded as adverse events probably related to treatment as were tachycardia and pallor with High THC. There were no other adverse events related to treatment.

A.3   SUBJECT 03

A.3.1   Baseline Findings

Subject 03 was a 38 year old female weighing 64.3 Kg and 175 cm tall. At pre study screen it was recorded that she had had three ectopic pregnancies followed by removal of fallopian tubes in 1991. No other medical history of note was recorded. She had taken cannabis first at about 16 years old and current use was approximately monthly.

The subject took five dose increments with THC:CBD, 1:1, six increments with High THC and the full eight increments with High CBD and placebo. Thus dosage per Kg of body weight was 0.194 mg for both THC and CBD with THC:CBD, 1:1, THC 0.223 mg with High THC and CBD 0.311 mg with High CBD (0.033 mg per increment for all treatments).

A.3.2   CANTAB Results

Spatial Working Memory

The range of between-errors made by this subject across all treatments was from 9 to 39. During treatment with THC:CBD, 1:1 the subject made 39 between-errors at three and eight hours, compared with only 17 between-errors at ten minutes. There was little change in performance across the ten minute and three hour time-point during treatment with High THC (24 versus 25 respectively), but with High CBD and placebo scores of 25 and 18 respectively at ten minutes were both followed by scores of 9 at three hours. The strategy score, however, remained relatively constant throughout all treatments.

Paired Associative Learning

For all treatments, the subject reached the end of the test, completing all stages successfully. The range of errors made across all treatments was 0 to 17. The subject made the highest number of errors (17) during treatment with High CBD at three hours.

Pattern Recognition Memory (immediate and delayed)

For all treatments, the subject was performing at near ceiling in the immediate recognition phase, scoring in the range 9 to 12. In the delayed recognition test, the subject made more errors during treatment with all active treatments compared with placebo.

Spatial Span

Across all treatments, the span length range was 5 to 8 boxes. The subject attained a span length of 5 at all time-points during treatment THC:CBD, 1:1 which was lower than the span lengths of 7 and 8 attained in the other conditions. However, performance appeared to improve steadily across treatment periods, suggesting a learning effect may have been operating, thus this finding should be viewed with caution.

Rapid Visual Information Processing

The range for the total number of hits made across all treatments was 21 to 27, although the lowest number of hits overall was made during the first treatment period with treatment THC:CBD, 1:1 at the eight hour time-point. Performance during the subsequent periods did not vary markedly between time-points and treatments.

A.3.3 Other Effects Including Safety

Times of effect

Table 11
Subject 03: Onset of effects by treatment

Variable	THC:CBD, 1:1	High THC	High CBD	Placebo
First effects apparent	26 mins	~32 mins	18 mins	-
Peak or plateau	~2 hours	-	-	-
Offset of effects if apparent	>3½ hours	-	-	-
Description of effects, if any	"Stoned in waves" Tired but otherwise normal at 8 hours	Relaxed and happy, "smooth"	Stomach cramps persisting at 8 hours	No effect apparent

Visual Analogue Scales (VAS): alertness

The pre-dose score ranged from 72 (THC:CBD, 1:1) to 93 (placebo) after which there was a perceived decrease in alertness in all periods, most marked at three hours. The lowest scores, indicating decreased alertness (with decrease from pre-dose) were rated as follows: High THC 39 (-33), THC:CBD, 1:1, 44 (-32), High CBD 62 (- 16) , placebo 75 (-18). Scores thereafter increased.

VAS: well-being

The pre-dose scores ranged from 87 with High CBD to 91 with High THC and the ensuing variation was not quantitatively marked (except for a decrease to 60 at eight hours with High CBD), indicating a positive feeling of well-being throughout.

VAS: mood

The pre-dose scores ranged from 82 with High CBD to 90 with High THC indicating good mood, and the variation thereafter was no more than ten points from pre-dose except with THC:CBD, 1;1, for which there was a decrease to 67 (-18) at ten minutes after final dose increment.

VAS Oral moisture

The pre-dose scores ranged from 37 to 96, and thereafter with all treatments lower scores, that is, increased dryness of mouth, were recorded until either eight or twelve hours.

VAS: hunger

The scores indicated a degree of hunger throughout, with the lowest scores recorded at three hours when they ranged from 0 with placebo to 14 with THC:CBD, 1:1. Hunger was relieved to some degree at eight and twelve hours (lunch was given at four hours, the main meal at nine hours).

Unpleasant effects

The majority of scores were 98 to 100 indicating an absence of unpleasant effects, except at twelve hours with THC:CBD,1:1, score: 95, and with High CBD, at eight hours: score: 80 and twelve hours, score 47. No comment was appended for THC:CBD, 1:1, but stomach cramps were noted at about eight hours with High CBD.

Conjunctival Reddening

No conjunctival reddening was noted with placebo. With all active treatments mild reddening was present from 15 (THC:CBD, 1:1) or 30 minutes after start of dose until after two (High CBD) or four hours, and with THC:CBD, 1:1 reached moderate intensity at two hours.

Vital signs

Pre study	Blood pressure	115/65	mmHg	Pulse rate:	74	beats per minute
Post study	Blood pressure	108/65	mmHg	Pulse rate:	76	beats per minute

This subject appeared to have a normal low resting blood pressure and no marked changes were noted throughout. The systolic rarely rose above 110 mmHg and the diastolic above 70 mmHg. Similarly the pulse rate (CRF record) was between 60 and 72 bpm with placebo and rarely rose above this range during the first four hours after dose with the active medication, except for rises to 84 bpm (one hour, GW0101SX01, THC:CBD, 1:1), and 88 bpm (45 minutes, GW1901SX01, High THC).

Related Adverse Events

This subject reported stomach cramps, possibly related to treatment, which commenced four and a half hours after start of High CBD dosing and persisted for ten and a half hours. There were no other adverse events related to treatment.

A.4 SUBJECT 04

A.4.1 Baseline Findings

Subject 04 was a 30 year old female weighing 60.4 Kg and 166 cm tall. No medical history of note was recorded. She first used cannabis at about 22 years of age and current use was irregular, the subject had used it approximately twice in the three months prior to screening.

The maximum dose was taken in each period and the dosage per Kg of body weight was 0.331 mg (0.041 mg per increment).

A.4.2 CANTAB Results

Spatial Working Memory

The range of between-errors made by this subject across all treatments was from 0 to 37. During treatment with THC:CBD, 1:1 the subject made 37 between-errors at three hours, compared with 30 between-errors at ten minutes. A marked decrease in performance was observed between ten minutes and three hours during treatment with High CBD (3 versus 31 between-errors respectively). The number of between-errors made during treatment with High THC, and placebo was relatively lower in comparison. The strategy score appeared to be higher, indicating poorer strategy utilisation, during the ten minute time-points High CBD and THC:CBD, 1;1 (37 and 39 respectively, compared to 29 and 34 with placebo and High THC respectively).

Paired Associative Learning

For all treatments, the subject reached the end of the test, completing all stages successfully. The range of errors made across all treatments was low overall, ranging from 0 to 4, thus no treatment appeared to have any significant effect.

Pattern Recognition Memory (immediate and delayed)

For all treatments, the subject was performing at near ceiling in the immediate recognition phase, scoring in the range of 11 to 12. In the delayed recognition test, the subject scored in the range 9 to 12 across all treatments, again showing no consistent pattern of impairment.

Spatial Span

Across all treatments, the span length range was 5 to 9 boxes. During treatment with THC:CBD, 1:1, the subject's performance decreased from a span length of 8 boxes at ten minutes to 5 at three hours. It then improved to a span length of 8 when measured at 8 hours. There were no such marked changes during the other treatment conditions.

Rapid Visual Information Processing

The range for the total number of hits made across all treatments was 19 to 27. The lowest number of hits overall was made during the first treatment period with treatment THC:CBD, 1:1 at the ten minutes time-point, after which performance between the different time-points and treatments did not vary significantly.

A.4.3   Other Effects Including Safety

Times of effect

Table 12
Subject 04: Onset of effects by treatment

Variable	THC:CBD, 1:1	High THC	High CBD	Placebo
First effects apparent	~1 hour 25 mins	45 mins	~55 mins	Nil apparent
Peak or plateau	~3 hours 40	2 hours 40 to 3 hours 10	-	-
Offset of effects if apparent	-	4 hours 25	4 to 5 hours	-
Description of effects, if any	-	Tachycardic at 3 hours	Very sleepy at ~3 hours	-
	-			-

Visual Analogue Scales (VAS): alertness

There was a perceived decrease in alertness in all periods, most marked at three and at either eight or twelve hours with the three active treatments. This contrasted with the placebo period, in which scores indicated an increase in alertness after dose which persisted until after eight hours. The most marked change from pre-dose was with THC:CBD, 1:1, with a score at three hours of 45 (40 points less than pre-dose), this was also the lowest score recorded throughout.

VAS: well-being

Only marginal change from the positive well-being recorded at pre-dose (range: 92 to 95) occurred except with THC:CBD, 1:1, in which the score fell by 19 points to 73 at ten minutes, thereafter increasing to 87 at three hours.

VAS: mood

The score ranged from 91 to 96 at pre-dose and changed little from this with High CBD or placebo although slightly lower scores indicating a decrease from 'wonderful' were recorded at eight hours for both (92 and 90 respectively). With THC:CBD, 1:1 there was a decrease to 85 at ten minutes and 84 at three hours, from a pre-dose of 91, and with High THC a decrease to 81 at three hours from a pre-dose of 96.

VAS: oral moisture

The majority of scores were within five points of pre-dose which ranged from 89 to 94, indicating slightly less than normal moisture. There were sharp decreases at three hours for both THC:CBD, 1:1 (score: 54) and High THC (score: 64) followed by return to approximate pre-dose values.

VAS: hunger

The pre-dose scores (range: 65 to 74) denoted a degree of hunger which intensified somewhat with all treatments from ten minutes to three hours and thereafter markedly relieved (compare with meal times). The exception was High THC, in which the scores increased from 66 to within five points of 90 (less hungry) for the remainder of the day.

VAS:unpleasant effects

The scores remained between 87 to 96 throughout, indicating that a marginal degree of unpleasant effects were experienced. There was one exception with THC:CBD 1:1 at three hours the score was 65. The accompanying comment suggested that peak effects were experienced approximately forty minutes after this but no description of the effects was recorded.

Conjunctival Reddening

No conjunctival reddening was noted with placebo. Mild reddening was present from between 30 minutes to four hours (THC:CBD,1:1) and from one hour after start of dose until after four hours (High CBD), and was intermittent from before 45 minutes until after four hours with High THC.

Vital signs

Pre study   Blood pressure   113/67   mmHg   Pulse rate: 67   beats per minute
Post study   Blood pressure   122/71   mmHg   Pulse rate: 81   beats per minute

The diastolic blood pressure was no higher than 68 mmHg and the pulse rate (CRF record) no higher than 72 with High CBD and a maximum of 91 bpm recorded with placebo at four hours. Higher rates were recorded intermittently with both the other active medications, notably a blood pressure of 121/86 mmHg and a pulse rate of 85 bpm at two hours after start of dose with THC:CBD, 1:1, and of 90/81 mmHg and 92 bpm at three hours after start of dose with High THC.

Related Adverse Events

Intermittent tachycardia reaching a maximum of 112 beats per minute was recorded from almost two hours after dosing with High THC for one and a half hours. This was of probable relationship and resolved without intervention.

A.5   SUBJECT 05

A.5.1   Baseline Findings

Subject 05 was a 34 year old male weighing 80 Kg and 172 cm tall. No medical history of note was recorded. He had commenced using cannabis at about age 17 and current use was approximately monthly.

The maximum dose was taken in each period and the dosage per Kg of body weight was 0.250 mg (0.031 mg per increment).

A.5.2   CANTAB Results

Spatial Working Memory

The range of between-errors made by this subject across all treatments was 0 to 39. Overall, the subject appeared to improve across treatment period, suggesting a learning effect. However, comparison of within-period time-points revealed significantly more between-errors at three hours compared to ten minutes and eight hours with THC:CBD, 1;1 and placebo. The strategy score remained relatively constant throughout all treatments.

Paired Associative Learning

For all treatments, the subject reached the end of the test, completing all stages successfully. The range of errors made across all treatments was low overall, ranging from 0 to 5 thus no treatment was observed to have any significant effect.

Pattern Recognition Memory (immediate and delayed)

For all treatments, the subject was performing at near ceiling in the immediate recognition phase. In the delayed recognition test, the subject scored in the range 11 to 12 across all treatments, showing no consistent pattern of impairment.

Spatial Span

Across all treatments, the span length range was 6 to 9 boxes. During treatment with THC:CBD, 1:1 the subject attained a span length of 6 boxes at 10 minutes, compared with 7 at 3 hours and 8 at 8 hours. There were no such marked changes with the other treatments.

Rapid Visual Information Processing

The range for the total number of hits made across all treatments was 23 to 27, the lowest number of hits being made at the first test session. The range of scores obtained was very small, and performance appeared relatively consistent across time-points and treatments.

A.5.3   Other Effects Including Safety

Times of effect

Table 13
Subject 05: Onset of effects by treatment

Variable	THC:CBD, 1:1	High THC	High CBD	Placebo
First effects apparent	35 min	58 mins	-	-
Peak or plateau	2 hours 10		-	-
Offset of effects if apparent	-		-	-
Description of effects, if any	Eyes watering, head getting heavy at 35 mins. Tired, mellow happy at 54 mins	Tired, very relaxed.	Nil apparent	Eyes watering at 50 mins
	-	Vivid, strange dreams overnight	-	-

Visual Analogue Scores (VAS): alertness

There was a perceived decrease in alertness with both THC:CBD, 1:1 and High THC. With THC:CBD the pre-dose score of 76 was followed by a decrease to 24 at ten minutes and to 18 at three hours. With High THC the pre-dose score of 63 was followed by scores of 29, 28 and at eight hours, 35. With both High CBD and placebo there was a contrasting increase in alertness by ten minutes after dose (from much lower pre-dose scores of 40 and 33 respectively). All scores were greater at twelve hours than at pre-dose.

VAS: well-being

There was a small increase in well-being with High CBD, from a pre-dose score of 79 to 87 at three hours, thereafter maintained. With the other three treatments there was a slight decrease from pre-dose score, which ranged from 82 to 90, by three hours. The decrease was most marked with THC:CBD, 1:1 at three hours (fall of 33 to 57). Increases were recorded by twelve hours except for THC:CBD, 1:1.

VAS: mood

The scores and the patterns of scoring were very similar to those for well-being with a small increase from pre dose score at three hours with High CBD and decreases recorded at either three or eight hours for the other three treatments.

VAS: oral moisture

The pre-dose score of 27 with THC:CBD, 1:1 denoted marked dryness of mouth. By 10 minutes after dose this had resolved to some extent (score; 68) and thereafter the pattern of scoring for this treatment was similar to that for High THC and placebo, with the lowest scores, and therefore the driest mouths, recorded at three hours. This was least marked with placebo. With High CBD there was an initial increase in dryness at ten minutes (fall of 10 to 80) followed by a return to approximate pre-dose scores.

VAS: hunger

There was a reduction from pre-dose score, and therefore an increase in hunger, for all treatments except High CBD at three hours. Increase in hunger was most marked with THC:CBD, 1:1 (fall of 22 to 26) and High THC (fall of 32 to 33). With High CBD there was an initial decrease in hunger from a pre-dose score of 68 to 82 at ten minutes, followed by a fall to 73 at three hours. All scores had increased at eight and twelve hours, following the meals.

VAS: unpleasant effects

The majority of scores were between 82 and 96, indicating slight unpleasant effects. There was however a lower score of 48 (fall of 45) at ten minutes with THC:CBD, 1:1. and accompanying comments of "eyes watering, head getting heavy" at 35 minutes after start of dose and "tired, mellow, happy" at 54 minutes after dose". There were decreases with placebo to scores of 79 and 75 at ten minutes and three hours. Watering eyes were recorded at 50 minutes.

Conjunctival Reddening

Mild reddening was noted prior to dose with all treatments except High CBD and was still present at 12 hours, the final assessment, for High THC and placebo. Moderate to severe reddening was noted with THC:CBD, 1:1, and High THC, with peaks at approximately four hours, and increase to moderate occurred with placebo from 45 to 60 minutes after start of dose.

Vital Signs

Pre study	Blood pressure	139/84	mmHg	Pulse rate:	59	beats per minute
Post study	Blood pressure	145/93	mmHg	Pulse rate:	68	beats per minute

The pulse rate for this subject was between 43 and 67 bpm (CRF record) throughout. The diastolic pressure tended to be high and indeed was above 90 mmHg at the majority of recordings made during the first hour after dosing with placebo, however, judging by the pre and post study recording this subject has a normal moderately high diastolic blood pressure, which reached 87 mmHg at times with all active medications but was noticeably higher throughout after dose with THC:CBD, 1:1, when a level of 141/101 mmHg was noted at 30 minutes and of 147/104 mmHg at 2 hours.

Related Adverse Events

This subject reported vivid dreams, probably related to treatment, overnight following all doses of active formulations. In addition, with THC:CBD, 1:11, severe conjunctival reddening was recorded from approximately one to six hours after start of dose and this was judged to be definitely related, whereas increased frequency of stool was possibly related. Intermittent pyrexia (high temperature) was possibly related to High THC although may have been associated with concurrent, unrelated common cold symptoms.

A.6   SUBJECT 06

A.6.1   Baseline Findings

Subject 06 was a 43 year old female weighing 69.1 Kg and 161 cm tall. No medical history of note other than removal of benign ovarian cysts in 1992, was recorded. She had commenced using cannabis at about 16 years old and had not used any for approximately 12 months.

The maximum dose was taken in each period and the dosage per Kg of body weight was 0.289 mg (0.036 mg per increment).

A.6.2   CANTAB Results

Spatial Working Memory

During treatment with THC:CBD, 1:1, in Period 1, the subject made 66 between-errors at three hours compared with 40 at ten minutes. However, during all other treatment conditions, the subject appeared to make less errors over time, suggesting a learning effect within each test session. The strategy score remained relatively constant throughout all treatments.

Paired Associative Learning

For all treatments, the subject reached the end of the test, completing all stages successfully. The range of errors made across all treatments was 0 to 35. The subject made the highest number of errors (35) during treatment with High CBD at three hours.

Pattern Recognition Memory (immediate and delayed)

For nearly all treatments, the subject was performing at near ceiling in the immediate recognition phase. However, the subject had a score of 8 out of 12 with High CBD at eight hours. In the delayed recognition test, the subject scored in the range 6 to 12, but there was no consistent pattern of impairment when compared with performance with placebo.

Spatial Span

Across all treatments, the span length range was 3 to 6 boxes. During treatment with High THC, the subject attained a span length of 3 boxes at ten minutes, compared with 4 at three hours and 5 at eight hours. Performance overall with High THC was slightly poorer than with other treatments where there were no such marked changes between time-points.

Rapid Visual Information Processing

The range for the total number of hits made across all treatments was 9 to 24, although the lowest number of hits (9) overall was made during the first treatment period with THC:CBD, 1;1, at three hours. The total number of hits made was higher overall with High CBD and placebo, ranging from 18 to 24, compared with a range of 9 to 18 with High THC and THC:CBD, 1:1, although a period effect may partly explain this as these two former treatments were administered in the third and fourth periods respectively.

A.6.3   Other Effects including Safety

Times of effect

Table 14
Subject 06: Onset of effects by treatment

Variable	THC:CBD, 1:1	High THC	High CBD	Placebo
First effects apparent	~1 hour 25	45 min	-	45 mins
Peak or plateau	-	1 hour 25	-	-
Offset of effects if apparent	-	6 hours 10	-	-
Description of effects, if any	Lightheaded, flying. Pulse rate transiently 91bpm	Lightheaded at 45 mins, "out of it" at 1 hour 5. "exaggerated sound at 1 hour 25. " nice and relaxed" at 6 hours 10	"Memory and concentration completely lost" during cognitive assessment at 3 hours. No other effect	"lightheaded" at 45 minutes. "Normal" at 2 hours 1 minute

Visual Analogue Scares (VAS): alertness

There was a perceived decrease in alertness with all treatments except placebo where slight increases were recorded (pre-dose 64, eight hours, 77). With THC:CBD, 1:1 there were cumulative decreases from a pre-dose of 94 to 53 at eight hours. The decrease with High THC was less marked, from a pre-dose of 75 to 54 at three hours and that with High CBD even slighter, from a pre-dose of 71 to 62 at three hours.

VAS: well-being

There was a continuous decrease in the well-being scores with THC:CBD, 1:1 from a pre-dose of 94 to 53 at twelve hours. There were also decreases with the other two active treatments but a slight increase with placebo.

VAS: mood

The scores and the pattern of the scoring were very similar to those for well-being. There was a continuous decrease in scores with THC:CBD, 1:1 from a pre-dose of 90 to 52 at twelve hours and less marked decreases at three hours for the other two active treatments, whereas there was a slight improvement in mood with placebo.

VAS: oral dryness

Scores indicated a marked increase in mouth dryness at three hours with both THC:CBD, 1:1 and High THC (falls of 58 to 32 and of 41 to 55 respectively). There was marginal change only with High CBD and placebo.

VAS:hunger

There were cumulative increases in hunger until three (or, with THC:CBD, 1:1 until eight) hours, of as much as 45 change from pre-dose score (with THC:CBD, 1:1), followed by at least partial return to pre-dose. With placebo the scores did not alter much from pre-dose (67) until an increase at eight hours which was maintained.

VAS: unpleasant effects

There was only marginal change from pre-dose scores with High CBD. With High THC and placebo there were marked drops at ten minutes only indicating the presence of some unpleasant effects (fall in score of 27 to 67, and of 29 to 67 respectively). The accompanying comments reported "light-headedness", feeling "out of it" and increased sensitivity to sound from 45 to 85 minutes after start of dose with High THC, and light-headedness with placebo. With THC:CBD, 1:1 there was a continuous decrease in score until eight hours (of 45 to 46)and again light-headedness was recorded from about 85 minutes after start of dose. Effects were noted on this occasion to have persisted for about ten hours.

Conjunctival Reddening

Mild reddening was present from 15 (THC:CBD, 1:1), 30 (High CBD) or 45 minutes(High THC, placebo) to after two hours or, for THC:CBD, 1:1, four hours.

Vital signs

Pre study   Blood pressure   115/69   mmHg   Pulse rate: 87   beats per minute
Post study   Blood pressure   123/81   mmHg   Pulse rate: 68   beats per minute

The diastolic pressure seldom rose above 80 mmHg and the pulse rate (CRF record) above 75 bpm. However a pulse rate of 91 bpm (blood pressure 127/82 mmHg) was recorded at 45 minutes after start of dose with THC:CBD, 1:1, and a blood pressure of 113/93 mmHg (pulse 68 bpm) at 30 minutes with High CBD.

Related Adverse Events

With High THC this female subject experienced three hot flushes considered possibly related to treatment, although it later became apparent to the Investigator that this subject was probably entering the menopause. Vivid dreams were reported with placebo.

CRR 300