CANNABIDIOL (CBD) FOR ADULTS WITH DRUG-RESISTANT EPILEPSY

HUMAN RESEARCH PROTOCOL

SPONSOR: CBD SAVES

LOCATION: LAS VEGAS, NEVADA
I. BACKGROUND AND SIGNIFICANCE

a. This study is sponsored by CBD Saves, a U.S. based non-profit research and educational organization. CBD Saves is sponsoring this study so there is specific evidence that cannabidiol is (or is not) effective as a treatment for adults with drug-resistant epilepsy. We believe this could be the first step towards building a body of research on how and why cannabidiol can be used to treat epilepsy. To date, there is only one clinical trial being conducted in the U.S. that studies marijuana and epilepsy (University of Colorado Denver).

b. Ancedotal reports on the antiepileptic properties of Marijuana are known since ancient times. Cannabidiol is the major neutral non-psychoactive cannabinoid in most Cannabis preparations. Since Brazilian workers Carlinin and Izquierdo first demonstrated the anticonvulsant effects of CBD in 1974, there have been several additional reports of the effectiveness of CBD. In addition to its favorable anticonvulsant effects and absence of toxicity, CBD seems to be devoid of psychotropic activity and other undesirable side effects in humans.

The earliest published clinical data were controlled trials of CBD in adult epilepsy. These findings support CBD Saves proposed study.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Patients</th>
<th>Daily Dose (mg)</th>
<th>Duration (weeks)</th>
<th>Efficacy (if reported)</th>
<th>Safety (if reported)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechoulan, R, Toward Drugs Derived from Cannabis (1978).</td>
<td>9 total 4 CBD 5 PBO</td>
<td>200 mg</td>
<td>12</td>
<td>CBD – 2 seizure free, 1 improved, 1 unchanged PBO - unchanged</td>
<td>No adverse events</td>
</tr>
<tr>
<td>Cunha, J, Chronic Administration of Cannabidiol to healthy volunteers and epileptic patients (1980).</td>
<td>15 total 7 CBD 8 PBO</td>
<td>200 – 300 mg</td>
<td>3-18</td>
<td>CBD – 4 seizure free PBO - 1 seizure free</td>
<td>N/A</td>
</tr>
<tr>
<td>Ames, F, Anticonvulsant effects of Cannabidiol (1986).</td>
<td>12 total 6 CBD 6 PBO</td>
<td>200 mg</td>
<td>4</td>
<td>N/A</td>
<td>Mild drowsiness</td>
</tr>
<tr>
<td>Tremblly, B, Double-blind clinical study of Cannabidiol as a secondary anticonvulsant (1990).</td>
<td>12 total 6 CBD 6 PBO</td>
<td>300 mg</td>
<td>24</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Although CBD Saves aims to study the effects of cannabidiol in adults (18-64) with drug-resistant epilepsy, there is increased interest amongst U.S. pediatric epilepsy specialists and patient organizations in the potential role of CBD in treating intractable childhood epilepsy, specifically Dravet syndrome. Case reports of its efficacy in severe refractory patients consistently provide encouraging signals. CBD’s “Natural” profile and safety data generated to date suggest that it could be an attractive treatment option without the unwanted side-effects of anti-seizure drugs. In 2013, there were promising study results from Jacobson and Porter of Stanford University. The method of the study consisted of surveying parents of children in the United States using CBD-enriched cannabis to control their intractable epilepsy. These parents were using a variety of non-approved and non-standardized “Artisanal” CBD preparations to control their children’s drug resistant seizures. Nineteen parents were surveyed to determine the effects of CBD on their children’s seizure frequency. Of the 19 children in the survey, 13 children had Dravet syndrome, four had Doose syndrome, and one each had LGS and idiopathic epilepsy. The average number of antiepileptic drugs tried before using CBD was 12. Sixteen (84%) of the 19 parents reported a reduction in their child's seizure frequency while taking CBD. Of these, two (11%) reported complete seizure freedom, eight (42%) reported a greater than 80% reduction in seizure frequency, and six (32%) reported a 25–60% seizure reduction.

c. CBD Saves is seeking to conduct this study to provide science and data to support the claim that cannabidiol reduces seizure activity in adults with drug-resistant epilepsy. So far, there have been many anecdotal reports of marijuana being used successfully to some degree in epilepsy. CBD Saves will benefit patients by treating conditions for which conventional medicines provide limited relief. CBD Saves will also benefit society by educating the public about the risks and benefits of Cannabis use.

II. SPECIFIC AIMS
   a. To investigate the potential antiepileptic effects of cannabidiol in adult patients with drug-resistant epilepsy.
   b. If cannabidiol reduces seizures for adults with drug resistant epilepsy then cannabidiol will be an effective adjunct therapy to (AEDs) in drug-resistant epilepsy.

III. SUBJECT SELECTION
    Key Inclusion Criteria:
    • Subject must be male or female aged between 18 and 64 years (inclusive).
    • Subject must have a documented history of drug-resistant epilepsy, which is not completely controlled by current antiepileptic drugs (AEDs).
• Subject must have experienced an epileptic seizure in the month prior to enrollment.
• Subject must be taking one or more antiepileptic drugs at a dose, which has been stable for at least four weeks.
• All medications or interventions for epilepsy (including ketogenic diet and vagus nerve stimulation) must have been stable for four weeks prior to screening.

Key Exclusion Criteria:
• Subject has a baseline function due to a modified Rankin score of 2 or greater.
• Subject has had a clinically significant illness in the four weeks prior to screening or randomization, other than epilepsy, that would contribute to psychogenic non-epileptic seizures.
• Subject is currently using or has in the past used recreational or medicinal cannabis and is unwilling to abstain from use during the duration of the study.
• Subject has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the investigational medicinal products.
• Subjects who have been part of a clinical trial involving another investigational cannabis product in the previous six months.
• There are plans for the subject to travel outside their country of residence during the study.

b. Candidates for participation will be 20 adults with drug-resistant epilepsy, having failed two chosen and tolerated antiepileptic drugs (AEDs) to control seizures when used for an adequate period of time. Subjects will be recruited via letters of referral sent to neurologists within the state of Nevada after IRB approved, contact within Epilepsy organizations, advertisements or announcements placed in appropriate locations or on appropriate internet sites and the sponsor site, and word of mouth. One of the staff will interview prospective subjects by telephone to learn if they meet basic eligibility criteria. If the prospective subject is interested in taking part in the study, the staff will provide them with consent materials for review and consideration. If, after review, an applicant remains interested in taking part in the study, then they will meet with one of the staff to complete the consent process.

IV: SUBJECT ENROLLMENT
a. All individuals who enter screening, as defined in this section, should be assigned a screening number and recorded on the “Subject screening log”. The subject screening number will also be noted on the subject’s informed consent form. Subjects who do not meet all screening criteria at screening will not be enrolled. A case report form (CRF) will not be completed for subjects who are not enrolled. These subjects will be documented only on the screening log and source records completed during screening. The study staff should record either the reason why an individual was not enrolled or the enrollment date and assigned subject number on this log. It is the responsibility of the staff to file this document in the staff site file (ISF) to be readily available for on-site monitoring and/or for inspection by the IRB or any authorized
b. The entire visit should take approximately 1.5 to 2.5 hours.
   i) Explain and obtain written informed consent from the subject. Written
   informed consent must be obtained prior to performing any study specific
   tests or evaluations.
   ii) Assign the subject a screening number. Complete the screening log.
   iii) Subjects will provide a medical and psychological history including
   documentation of any EEG’s taken within the past five years.
   iv) The staff will perform the relevant portions of the structured clinical interview
   for diagnosis to assess study eligibility.
   v) Staff will determine the optimal therapeutic dose (OTD).
      
      (0.5 mg x patient’s current weight (lb) = mg per day broken into 3 doses)
   vi) If the staff concludes the subject is eligible for the study, a physician will
   perform a neurological exam.
   vii) A qualitative urine screening will be taken to further support abstinence of
   marijuana use within one month prior to the start of the study.
   viii) If upon examination, there are questions raised about possible comorbid
   medical conditions that may affect study results, the staff will request a review of
   the subject’s medical records and request additional tests or assessments as
   indicated.
   ix) After eligibility is confirmed the subject will be enrolled and issued a subject
   identification number.
   x) If the subject continues to meet all inclusion criteria and no exclusion criteria,
   the staff will schedule introductory sessions and determine the beginning period
   of active dosing.

b. Randomization will occur prior to the day of the first introductory session. The
   subject’s screening number will be used in place of their name to further ensure
   the study remains blinded. All of the screening numbers will be written on small
   pieces of paper, folded and placed in a fish bowl to be drawn out like a raffle.
   Once all subjects have been assigned a group, the staff will contact them to
   schedule introductory sessions. During the introductory session the staff will:
   i) Administer one dose (25 mg/ml) of cannabidiol (CBD) or placebo.
   ii) Inquire about any possible changes in health for the subject.
   iii) Obtain from the subject the name and telephone number of an emergency
   contact for use throughout the study.
   iv) The staff will discuss locating another person who resides with the subject to
   verify appropriate use of cannabidiol and lack of diversion. The subject will
   provide the staff with a telephone number to use to reach the secondary
   verifier (“observer and witness”).
   v) The subject will undergo two one-hour introductory sessions with the staff,
   preferable on two consecutive days. The staff will provide the subject with
information about cannabidiol, including expected psychoactive and physical effects and a standardized procedure for ingesting cannabidiol (dosing).

vi) The staff will introduce the subject to the daily diary and will instruct them on a diary entry completion.

vii) Subjects will receive a research identification card ("wallet card") stating that they are a research subject and may test positive for drugs and listing staff contact information and instructions on how and when to present the card.

viii) Subjects will either arrange a ride from the study site to their home or current place of residence or the investigators will assist them in finding a means of transport from the study site.

ix) The subject is required to self-administer cannabidiol using the method of administration and potency the subject has assigned to use.

x) At the end of the second introductory session, the staff will provide the subject with a supply of cannabidiol intended to last for one month of the four-month self-administration period, and a lockable storage box with private combination lock. The subject will be instructed to use no more than three doses of cannabidiol per day.

xi) The staff will provide the subject with a daily cannabidiol use diary.

V: STUDY PROCEDURES

a. Efficacy and safety will be measured via monthly clinical visits and daily telephone status checks. The staff and subject will complete a weekly clinical evaluation of drug treatment using a scale with score 0-3 (0 - complete improvement, 1 - partial improvement, 2 - small improvement, 3 – without improvement). Upon completion of the dosing phase, the subject will have a hair sample taken for testing to determine their THC/cannabinoid levels over the past 120 days. The test results will be analyzed during the follow-up phase of the study.

b. • Drug: CBD001

CBD001 is an oral solution presented as an oily solution containing 1 ounce of cannabidiol (CBD: ACDC01). Laboratory analysis states the sample contains 12.5 mg/ml CBD and approximately .53 mg/ml THC in the 1 ounce sample. Cannabinoid potency analysis is 1.58% CBD and .07% THC. The CBD:THC ratio is 20:1, or 19% CBD and 1% THC.

i) Other Name: Cannabidiol

• Drug: Placebo control

An oral solution presented as an oily solution containing 1 ounce of olive oil.

i) Other Name: Placebo

• Method: The drug will be taken orally and is recommended to mix with water, ginger tea or juice.
• Schedule of administration: The subject will orally ingest the drug 3 times per day, preferably on an empty stomach. The subject must continue to follow the administration of prescribed medication they were taking before and during the experiment. CBD has no signs of toxicity or serious side effects when administered with prescription medication.

• Dose modifications: There will be four phases of dosing for subjects during the 4 month clinical trial.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Weeks</th>
<th>mg/150 lb./day</th>
<th>mg/day</th>
<th>doses per day</th>
<th>ml per day</th>
<th>ml per dose</th>
<th>ml per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>(1-4)</td>
<td>0.5 *150 = 75</td>
<td>3</td>
<td>5.73</td>
<td>1.9</td>
<td>40.1</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>(5-8)</td>
<td>1 *150 = 150</td>
<td>3</td>
<td>11.5</td>
<td>3.8</td>
<td>80.3</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>(9-12)</td>
<td>1.5 *150 = 225</td>
<td>3</td>
<td>17.2</td>
<td>5.7</td>
<td>120.4</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>(13-16)</td>
<td>2 *150 = 300</td>
<td>3</td>
<td>22.9</td>
<td>7.6</td>
<td>160.6</td>
<td></td>
</tr>
</tbody>
</table>

c. No devices will be used besides 2, 5 and 10 ml syringes, a urinary drug screen and hair testing device.

d. No procedures or surgical interventions are scheduled for this study.

e. Data will be collected throughout the screening process, introductory sessions, daily telephone contact and weeks during cannabidiol self-administration.

VI: BIOSTATISTICAL ANALYSIS

a. Daily cannabidiol use diary (120 entries)

  Clinical evaluation of drug treatment

  [Time Frame: Weekly ] [Scored 0-3, 0 – complete improvement, 1 – partial improvement, 2 – small improvement, 3 – without improvement].

b. Mean percentage change from baseline to the end of treatment in seizure frequency.

i) Number of subjects who experienced a 50% or more reduction in seizures from baseline.

ii) Mean change from baseline in the Quality of Life in Epilepsy (QOLE) score

  [Time Frame: 0-16 weeks] [Designated as safety issue: No]

  (1) The QOLE is composed of 16 subscales assessing seven domains of Health Related Quality of Life (physical function, social function, emotional well-being, cognition, behavior, general health and general quality of life).

c. The proposed study is intended to gather data on the safety and efficacy of cannabidiol in adults with drug-resistant epilepsy. Because this study is in a small sample, statistical power is difficult to assess. This study will be the first to examine the effects of cannabidiol on drug-resistant epilepsy and the literature does not permit a basis for calculating actual effect size for any study effect.
VII: RISKS AND DISCOMFORTS
   a. This study does not involve surgical procedures so there are no complications posed. Although there is extensive literature on the risks of habitual marijuana use in humans including adverse events, there is no information on the risks associated with cannabidiol dependency. CBD does not appear to have any toxic effects on humans when administered at the above dosage over a long period. Recent findings conclude that cannabidiol provides many therapeutic benefits. Cannabidiol is non-psychoactive so it does not alter mood and perception like Marijuana. Patients with marijuana dependency ultimately develop psychosis and impaired memory.

   b. Drug side effects are relatively non-existent besides drowsiness and fatigue.

   c. Cannabidiol will be self-administered through a pre-measured syringe three times a day.

   d. Although cannabidiol is non-psychoactive, Marijuana is associated with acute risks as well as risks of continued daily use. Chief amongst these are unwanted psychological effects, including anxiety or paranoia, cardiovascular and pulmonary effects, impaired driving and abuse liability. The staff will address a number of risks by enrolling subjects without contradicting conditions, including psychogenic non-epileptic seizures. Subjects who pose a major suicide risk will not be enrolled in the study. Subjects who have smoked or otherwise ingested marijuana in the month prior to enrollment will not be enrolled in the study. Neither will any subject that the staff or medical monitor believes has contradicting history of or current substance abuse or dependence.

   e. There are no Radiation risks involved in this study and a statement from the Radiation Safety Committee can easily be obtained.

VIII: POTENTIAL BENEFITS
   a. Evidence that CBD is (or is not) effective as a treatment for adults with drug-resistant epilepsy.

   b. Reduction in seizures, antiepileptic drug (AED) dependency and overall improvement in quality of life.

   c. Increased understanding and public acceptance of cannabidiol as potential treatment for forms of epilepsy. Future studies with higher enrollment rates and FDA approval of cannabidiol derived drugs.

IX: MONITORING AND QUALITY ASSURANCE
   a. The entire staff will be trained prior to the start of the protocol by the sponsor’s clinical research staff. The clinical study site will be monitored by site visits and remote communication to the staff by representatives of the sponsor. The site will be monitored as appropriate for the rate of enrollment. During each monitoring
visit, source data verification will be performed by a Clinical Research Associate (CRA) to ensure compliance, including accurate and complete recording of data on CRFs, source documents, and drug accountability records. A CRF collation supplied by the sponsor will be completed for each subject enrolled. Monitoring and auditing procedures of the sponsor will be followed, in order to comply with Good Clinical Practice (GCP) guidelines and to ensure validity of the study data. The sponsor will review the study documentation used for planning, conducting and monitoring of the study in order to ensure compliance with GCP and local regulations. This documentation includes at minimum: the Investigator’s Brochure, the Study Protocol, the Case Report Forms and the Subject Information and Consent Form. During or after the clinical protocol, the regulatory authorities, the IRB, and/or representatives of the sponsor may request access to all source documents, CRFs and other protocol documentation for on-site audit or inspection.

b. The Data Safety Monitoring Board will assist with safety monitoring throughout the study to ensure information collected through self-administration reports and clinical sessions is assessed properly.

c. In order to monitor outcomes, subjects will meet with the staff for monthly clinical evaluations. During that time, the staff and subject will complete a clinical evaluation of treatment. The staff will review the subject’s cannabidiol (CBD) use diary and a phone log to ensure the subject has called in the appropriate amount of times to confirm their medicine has been taken. All outcomes will be monitored by comparing the subject’s current progress with the starting baseline. A quality of life in epilepsy score will be generated. The QOLE is composed of 16 subscales assessing seven domains of Health Related Quality of Life (physical function, social function, emotional well-being, cognition, behavior, general health and general quality of life).

d. A hair sample will be taken during the final phase of the study to test the subject’s THC/Cannabinoid levels over the past 120 days. This data will be analyzed during the follow up phase of the study.

e. An Adverse Event (AE) is defined as any untoward or unfavorable medical occurrence in a clinical research study subject, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subjects' involvement in the research, whether or not considered related to participation in the research. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions. An unexpected adverse event is one that is not listed in the current Investigator’s Brochure or an event that is by nature more specific or more severe than a listed event. All AEs will be monitored by the staff until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the protocol, a clinical assessment will be made by the staff and/or Medical
Monitor as to whether continued follow-up of the AE is warranted.

The severity of events reported on the “Adverse Events” CRF will be determined by the staffs:

Mild: no limitation in normal daily activity
Moderate: some limitation in normal daily activity
Severe: unable to perform normal daily activity

The relationship of the study treatment to an AE will be determined by the staff based on the following definitions:

1. Not Related
   The AE is not related if exposure to the investigational product has not occurred, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the investigational product, i.e. there are no facts (evidence) or arguments to suggest a causal relationship, or the AE is more likely related to the subject’s pre-existing condition.

2. Possibly Related
   The administration of the investigational product and the AE are considered reasonably related in time and the AE could be explained by causes other than exposure to the investigational product.

3. Probably Related
   Exposure to the investigational product and AE are reasonably related in time and the investigational product is more likely than other causes to be responsible for the AE, or is the most likely cause of the AE.
   The relationship of the study treatment to an AE will be determined by the investigator.

All SAEs will be collected for the duration of the study. All SAEs which occur during the course of the trial, whether considered to be associated with the study drug or not, have to be reported within 24 hours or at the latest on the following working day by telephone or fax to the principal investigator.
IX: REFERENCES

1. Potts, Richard, A Double Blind, Placebo Controlled Two-part Study to Investigate the Dose-ranging Safety and Pharmacokinetics, Followed by the Efficacy and Safety of Cannabidiol (GWP42003-P) in Children and Young Adults With Dravet Syndrome. GW Pharmaceuticals LTD., 2014

2. Weltman, Martin PhD MD, Cannabidiol (CBD) for the Management of Cannabis Withdrawal: A Phase II Proof of Concept Study. The University of New South Wales, 2014


8. Cunha, J, Chronic Administration of Cannabidiol to healthy volunteers and epileptic patients (1980).
