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(54) Title: USE OF CANNABIDIOL IN THE TREATMENT OF SEIZURES ASSOCIATED WITH JEAVON'S SYNDROME

(57) Abstract: The present invention relates to the use of cannabidiol (CBD) for the treatment of seizures associated with rare epilepsy syndromes. In particular the seizures associated with rare epilepsy syndromes that are treated are those which are experienced in patients diagnosed with Jeavon's syndrome. In a further embodiment the types of seizures include absence, myoclonic-absence, myoclonic, focal seizures without impairment and focal seizures with secondary generalisation. Preferably the dose of CBD is between 5 mg/kg/day to 50 mg/kg/day.

USE OF CANNABIDIOL IN THE TREATMENT OF SEIZURES ASSOCIATED WITH JEAVON'S SYNDROME

FIELD OF THE INVENTION

[0001] The present invention relates to the use of cannabidiol (CBD) for the treatment of seizures associated with rare epilepsy syndromes. In particular the seizures associated with rare epilepsy syndromes that are treated are those which are experienced in patients diagnosed with Jeavon's syndrome. In a further embodiment the types of seizures include absence, myoclonic-absence, myoclonic, focal seizures without impairment and focal seizures with secondary generalisation. Preferably the dose of CBD is between 5 mg/kg/day to 50 mg/kg/day.

[0002] In a further embodiment the CBD used is in the form of a highly purified extract of cannabis such that the CBD is present at greater than 95% of the total extract (w/w) and the cannabinoid tetrahydrocannabinol (THC) has been substantially removed, to a level of not more than 0.15% (w/w).

[0003] Preferably the CBD used is in the form of a botanically derived purified CBD which comprises greater than or equal to 98% (w/w) CBD and less than or equal to 2% (w/w) of other cannabinoids. More preferably the other cannabinoids present are THC at a concentration of less than or equal to 0.1% (w/w); CBD-C1 at a concentration of less than or equal to 0.15% (w/w); CBDV at a concentration of less than or equal to 0.8% (w/w); and CBD-C4 at a concentration of less than or equal to 0.4% (w/w). The botanically derived purified CBD preferably also comprises a mixture of both trans-THC and cis-THC. Alternatively, a synthetically produced CBD is used.

[0004] Most preferably the other cannabinoids present are THC at a concentration of about 0.01% to about 0.1% (w/w); CBD-C1 at a concentration of about 0.1% to about 0.15% (w/w); CBDV at a concentration of about 0.2% to about 0.8% (w/w); and CBD-C4 at a concentration of about 0.3% to about 0.4% (w/w). Most preferably still the THC is present at a concentration of about 0.02% to about 0.05% (w/w).

[0005] Where the CBD is given concomitantly with one or more other anti-epileptic drugs (AED), the CBD may be formulated for administration separately, sequentially or simultaneously with one or more AED or the combination may be provided in a single dosage form.

BACKGROUND TO THE INVENTION

[0006] Epilepsy occurs in approximately 1% of the population worldwide, (Thurman *et al.*, 2011) of which 70% are able to adequately control their symptoms with the available existing anti-epileptic drugs (AED). However, 30% of this patient group, (Eadie *et al.*, 2012), are unable

to obtain seizure freedom from the AED that are available and as such are termed as suffering from intractable or "treatment-resistant epilepsy" (TRE).

[0007] Intractable or treatment-resistant epilepsy was defined in 2009 by the International League Against Epilepsy (ILAE) as "*failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom*" (Kwan *et al.*, 2009).

[0008] Individuals who develop epilepsy during the first few years of life are often difficult to treat and as such are often termed treatment resistant. Children who undergo frequent seizures in childhood are often left with neurological damage which can cause cognitive, behavioral and motor delays.

[0009] Childhood epilepsy is a relatively common neurological disorder in children and young adults with a prevalence of approximately 700 per 100,000. This is twice the number of epileptic adults per population.

[0010] When a child or young adult presents with a seizure, investigations are normally undertaken in order to investigate the cause. Childhood epilepsy can be caused by many different syndromes and genetic mutations and as such diagnosis for these children may take some time.

[0011] The main symptom of epilepsy is repeated seizures. In order to determine the type of epilepsy or the epileptic syndrome that a patient is suffering from an investigation into the type of seizures that the patient is experiencing is undertaken. Clinical observations and electroencephalography (EEG) tests are conducted and the type(s) of seizures are classified according to the ILEA classification.

[0012] Generalized seizures, where the seizure arises within and rapidly engages bilaterally distributed networks, can be split into six subtypes: tonic-clonic (grand mal) seizures; absence (petit mal) seizures; clonic seizures; tonic seizures; atonic seizures and myoclonic seizures.

[0013] Focal (partial) seizures where the seizure originates within networks limited to only one hemisphere, are also split into sub-categories. Here the seizure is characterized according to one or more features of the seizure, including aura, motor, autonomic and awareness / responsiveness. Where a seizure begins as a localized seizure and rapidly evolves to be distributed within bilateral networks this seizure is known as a bilateral convulsive seizure, which is the proposed terminology to replace secondary generalized seizures (generalized seizures that have evolved from focal seizures and are no longer remain localized).

[0014] Focal seizures where the subject's awareness / responsiveness is altered are referred to as focal seizures with impairment and focal seizures where the awareness or responsiveness of the subject is not impaired are referred to as focal seizures without impairment.

[0015] Jeavon's syndrome is a rare type of epilepsy. It is sometimes referred to as epilepsy with eyelid myoclonia. It is one of the most distinctive reflex syndromes of idiopathic generalized epilepsy characterized by the triad of eyelid myoclonia with and without absences, eye-closure-induced seizures, EEG paroxysms, or both, and photosensitivity. Eyelid myoclonia with or without absences is a form of epileptic seizure manifesting with myoclonic jerks of the eyelids with or without a brief absence. These are mainly precipitated by closing of the eyes and lights. Eyelid myoclonia is the defining seizure type of Jeavon's syndrome.

[0016] Anti-epileptic drugs including valproic acid, lamotrigine and ethosuximide may help treat seizures in Jeavon's syndrome. Levetiracetam and clobazam may also be helpful.

[0017] Cannabidiol (CBD), a non-psychoactive derivative from the cannabis plant, has demonstrated anti-convulsant properties in several anecdotal reports, pre-clinical and clinical studies both in animal models and humans. Three randomized control trials showed efficacy of the purified pharmaceutical formulation of CBD in patients with Dravet and Lennox-Gastaut syndrome.

[0018] Based on these three trials, a botanically derived purified CBD preparation was approved by FDA in June 2018 for the treatment of seizures associated with Dravet and Lennox-Gastaut syndromes.

[0019] The patent EP3157512 describes using CBD to treat a number of different childhood epilepsy syndromes one of which is listed is Jeavon's syndrome. There are no data in the patent which demonstrate or suggest that the use of CBD may be efficacious in the treatment of seizures associated with Jeavon's syndrome. Example 1 demonstrates use of CBD was able to reduce absence seizures whilst Example 2 provides efficacy of the CBD in treating myoclonic absence seizures.

[0020] A paper published in 2018 describes the use of artisanal preparations of CBD in the treatment of epilepsy. A cohort of 108 patient records were reviewed, one patient was reported to suffer from Jeavon's syndrome. Again, there is no teaching in this document to demonstrate or suggest that treatment with an artisanal preparation of CBD was effective in the treatment of Jeavon's syndrome[1].

[0021] GB 2568929 describes the concurrent use of CBD and an immunosuppressant drug in the treatment of childhood-onset epilepsy syndromes one of which is listed is Jeavon's syndrome. There are no data in the patent application which demonstrate or suggest that the use of CBD may be efficacious in the treatment of seizures associated with Jeavon's syndrome.

[0022] GB 2539472 and GB 2569961 both disclose the use of highly purified CBD for the treatment of various types of seizures, but do not show any data to suggest efficacy in the treatment of Jeavon's syndrome

[0023] The applicant has found by way of an open label, expanded-access program that treatment with CBD resulted in a significant reduction in specific seizure types including

absence, myoclonic-absence, myoclonic, and focal seizures with secondary generalisation in patients diagnosed with Jeavon's syndrome.

BRIEF SUMMARY OF THE DISCLOSURE

[0024] In accordance with a first aspect of the present invention there is provided a cannabidiol (CBD) preparation for use in the treatment of seizures associated with Jeavon's syndrome.

[0025] In a further embodiment the seizures associated with Jeavon's syndrome are absence, myoclonic-absence, myoclonic, focal seizures without impairment and focal seizures with secondary generalisation.

[0026] In a further embodiment, the CBD preparation comprises greater than 95% (w/w) CBD and not more than 0.15% (w/w) tetrahydrocannabinol (THC).

[0027] Preferably the CBD preparation comprises greater than or equal to 98% (w/w) CBD and less than or equal to 2% (w/w) other cannabinoids, wherein the less than or equal to 2% (w/w) other cannabinoids comprise the cannabinoids tetrahydrocannabinol (THC); cannabidiol-C1 (CBD-C1); cannabidivarin (CBDV); and cannabidiol-C4 (CBD-C4), and wherein the THC is present as a mixture of trans-THC and cis-THC.

[0028] Preferably the CBD preparation is used in combination with one or more concomitant anti-epileptic drugs (AED).

[0029] Preferably the one or more AED is selected from the group consisting of: valproic acid, clobazam, lamotrigine, zonisamide and ethosuximide.

[0030] In one embodiment the CBD is present is isolated from cannabis plant material. Preferably at least a portion of at least one of the cannabinoids present in the CBD preparation is isolated from cannabis plant material.

[0031] In a further embodiment the CBD is present as a synthetic preparation. Preferably at least a portion of at least one of the cannabinoids present in the CBD preparation is prepared synthetically.

[0032] Preferably the dose of CBD is greater than 5 mg/kg/day. More preferably the dose of CBD is 20 mg/kg/day. More preferably the dose of CBD is 25 mg/kg/day. More preferably the dose of CBD is 50 mg/kg/day.

[0033] In accordance with a second aspect of the present invention there is provided a method of treating seizures associated with Jeavon's syndrome comprising administering a cannabidiol (CBD) preparation to the subject in need thereof.

DEFINITIONS

[0034] Definitions of some of the terms used to describe the invention are detailed below:

[0035] Over 100 different cannabinoids have been identified, see for example, Handbook of Cannabis, Roger Pertwee, Chapter 1, pages 3 to 15. These cannabinoids can be split into different groups as follows: Phytocannabinoids; Endocannabinoids and Synthetic cannabinoids (which may be novel cannabinoids or synthetically produced phytocannabinoids or endocannabinoids).

[0036] "Phytocannabinoids" are cannabinoids that originate from nature and can be found in the cannabis plant. The phytocannabinoids can be isolated from plants to produce a highly purified extract or can be reproduced synthetically.

[0037] "Highly purified cannabinoids" are defined as cannabinoids that have been extracted from the cannabis plant and purified to the extent that other cannabinoids and non-cannabinoid components that are co-extracted with the cannabinoids have been removed, such that the highly purified cannabinoid is greater than or equal to 95% (w/w) pure.

[0038] "Synthetic cannabinoids" are compounds that have a cannabinoid or cannabinoid-like structure and are manufactured using chemical means rather than by the plant.

[0039] Phytocannabinoids can be obtained as either the neutral (decarboxylated form) or the carboxylic acid form depending on the method used to extract the cannabinoids. For example, it is known that heating the carboxylic acid form will cause most of the carboxylic acid form to decarboxylate into the neutral form.

[0040] "Treatment-resistant epilepsy" (TRE) or "intractable epilepsy" is defined as per the ILAE guidance of 2009 as epilepsy that is not adequately controlled by trials of one or more AED.

[0041] "Myoclonic seizures" are characterised by a 'muscle jerk'. Myoclonic seizures are brief but can happen in clusters (many happening close together in time) and often happen shortly after waking. In myoclonic seizures the person is conscious, but they are classified as generalised seizures.

[0042] "Myoclonic-absence seizures" are characterised by the patient's neck, back, and arms become stiff or rigid (tonic contraction). There is ratchet-like jerking of the head, arms, and legs. The patient is not aware and has a staring facial expression. The loss of awareness might be subtle and hard to notice.

[0043] "Absence seizures" also may be called a "petit mal" these types of seizure cause a loss

of awareness for a short time. They mainly affect children although can happen at any age. During an absence seizure, a person may: stare blankly into space; look like they are "daydreaming"; flutter their eyes; make slight jerking movements of their body or limbs. The seizures usually only last up to 15 seconds and may occur several times a day.

[0044] "Focal Seizures" are defined as seizures which originate within networks limited to only one hemisphere. What happens during the seizure depends on where in the brain the seizure happens and what that part of the brain normally does.

[0045] "Focal seizure with secondary generalisation" seizures start in a limited area on one side of the brain and spread to involve both sides. This is different from a generalized onset seizure, which starts on both sides of the brain.

DETAILED DESCRIPTION

PREPARATION OF HIGHLY PURIFIED CBD EXTRACT

[0046] The following describes the production of the highly-purified (>95% w/w) cannabidiol extract which has a known and constant composition.

[0047] In summary the drug substance used is a liquid carbon dioxide extract of high-CBD containing chemotypes of *Cannabis sativa* L. which had been further purified by a solvent crystallization method to yield CBD. The crystallisation process specifically removes other cannabinoids and plant components to yield greater than or equal to 95% CBD. Although the CBD is highly purified because it is produced from a cannabis plant rather than synthetically there is a small number of other cannabinoids which are co-produced and co-extracted with the CBD. Details of these cannabinoids and the quantities in which they are present in the medication are as described in Table A below.

Table A: Composition of highly purified CBD extract

Cannabinoid	Concentration
CBD	> 95% w/w
CBDA	NMT 0.15% w/w
CBDV	NMT 1.0% w/w
Δ^9 THC	NMT 0.15% w/w
CBD-C4	NMT 0.5% w/w

> – greater than

NMT – not more than

PREPARATION OF BOTANICALLY DERIVED PURIFIED CBD

[0048] The following describes the production of the botanically derived purified CBD which comprises greater than or equal to 98% w/w CBD and less than or equal to other cannabinoids was used in the open label, expanded-access program described in Example 1 below.

[0049] In summary the drug substance used in the trials is a liquid carbon dioxide extract of high-CBD containing chemotypes of *Cannabis sativa* L. which had been further purified by a solvent crystallization method to yield CBD. The crystallisation process specifically removes other cannabinoids and plant components to yield greater than 95% CBD w/w, typically greater than 98% w/w.

[0050] The *Cannabis sativa* L. plants are grown, harvested, and processed to produce a botanical extract (intermediate) and then purified by crystallization to yield the CBD (botanically derived purified CBD).

[0051] The plant starting material is referred to as Botanical Raw Material (BRM); the botanical extract is the intermediate; and the active pharmaceutical ingredient (API) is CBD, the drug substance.

[0052] All parts of the process are controlled by specifications. The botanical raw material specification is described in Table B and the CBD API is described in Table C.

Table B: CBD botanical raw material specification

Test	Method	Specification
Identification: -A -B -C	 Visual TLC HPLC/UV	 Complies Corresponds to standard (for CBD & CBDA) Positive for CBDA
Assay: CBDA + CBD	In-house (HPLC/UV)	NLT 90% of assayed cannabinoids by peak area
Loss on Drying	Ph.Eur.	NMT 15%
Aflatoxin	UKAS method	NMT 4ppb
Microbial: - TVC - Fungi - E.coli	Ph.Eur.	NMT10^7cfu/g NMT10^5cfu/g NMT10^2cfu/g
Foreign Matter:	Ph.Eur.	NMT 2%
Residual Herbicides and Pesticides	Ph.Eur.	Complies

Table C: Specification of an exemplary botanically derived purified CBD preparation

Test	Test Method	Limits
Appearance	Visual	Off-white / pale yellow crystals
Identification A	HPLC-UV	Retention time of major peak corresponds to certified CBD Reference Standard
Identification B	GC-FID/MS	Retention time and mass spectrum of major peak corresponds to certified CBD Reference Standard
Identification C	FT-IR	Conforms to reference spectrum for certified CBD Reference Standard
Identification D	Melting Point	65 - 67°C
Identification E	Specific Optical Rotation	Conforms with certified CBD Reference Standard; -110° to -140° (in 95% ethanol)
Total Purity	Calculation	≥ 98.0%
Chromatographic Purity 1	HPLC-UV	≥ 98.0%
Chromatographic Purity 2	GC-FID/MS	≥ 98.0 %
CBDA CBDV THC CBD-C4	HPLC-UV	NMT 0.15% w/w 0.2-1.0% w/w 0.01-0.1% w/w 0.3-0.5% w/w
Residual Solvents: Alkane Ethanol	GC	 NMT 0.5% w/w NMT 0.5% w/w
Residual Water	Karl Fischer	NMT 1.0% w/w

[0053] The purity of the botanically derived purified CBD preparation was greater than or equal to 98%. The botanically derived purified CBD includes THC and other cannabinoids, e.g., CBDA, CBDV, CBD-C1, and CBD-C4.

[0054] In some embodiments, the CBD preparation comprises not more than 0.15% THC based on total amount of cannabinoid in the preparation. In some embodiments, the CBD preparation comprises about 0.01% to about 0.1% THC based on total amount of cannabinoid in the preparation. In some embodiments, the CBD preparation comprises about 0.02% to about 0.05% THC based on total amount of cannabinoid in the preparation.

[0055] In some embodiments, the CBD preparation comprises about 0.2% to about 1.0% CBDV based on total amount of cannabinoid in the preparation. In some embodiments, the CBD preparation comprises about 0.2% to about 0.8% CBDV based on total amount of cannabinoid in the preparation.

[0056] In some embodiments, the CBD preparation comprises about 0.3% to about 0.5% CBD-C4 based on total amount of cannabinoid in the preparation. In some embodiments, the

CBD preparation comprises about 0.3% to about 0.4% CBD-C4 based on total amount of cannabinoid in the preparation.

[0057] In some embodiments, the CBD preparation comprises about 0.1% to about 0.15% CBD-C1 based on total amount of cannabinoid in the preparation.

[0058] Distinct chemotypes of the *Cannabis sativa* L. plant have been produced to maximize the output of the specific chemical constituents, the cannabinoids. Certain chemovars produce predominantly CBD. Only the (-)-trans isomer of CBD is believed to occur naturally. During purification, the stereochemistry of CBD is not affected.

Production of CBD botanical drug substance

[0059] An overview of the steps to produce a botanical extract, the intermediate, are as follows:

a) Growing
b) Direct drying
c) Decarboxylation
d) Extraction - using liquid CO_2
e) Winterization using ethanol
f) Filtration
g) Evaporation

[0060] High CBD chemovars were grown, harvested, dried, baled and stored in a dry room until required. The botanical raw material (BRM) was finely chopped using an Apex mill fitted with a 1 mm screen. The milled BRM was stored in a freezer prior to extraction.

[0061] Decarboxylation of CBDA to CBD was carried out using heat. BRM was decarboxylated at 115ºC for 60 minutes.

[0062] Extraction was performed using liquid CO_2 to produce botanical drug substance (BDS), which was then crystalized to produce the test material. The crude CBD BDS was winterized to refine the extract under standard conditions (2 volumes of ethanol at -20°C for approximately 50 hours). The precipitated waxes were removed by filtration and the solvent was removed to yield the BDS.

Production of botanically derived purified CBD preparation

[0063] The manufacturing steps to produce the botanically derived purified CBD preparation from BDS were as follows:

a) Crystallization using C_5-C_{12} straight chain or branched alkane
b) Filtration

c) Vacuum drying

[0064] The BDS produced using the methodology above was dispersed in C_5-C_{12} straight chain or branched alkane. The mixture was manually agitated to break up any lumps and the sealed container then placed in a freezer for approximately 48 hours. The crystals were isolated via vacuum filtration, washed with aliquots of cold C_5-C_{12} straight chain or branched alkane, and dried under a vacuum of <10mb at a temperature of 60°C until dry. The botanically derived purified CBD preparation was stored in a freezer at -20°C in a pharmaceutical grade stainless steel container, with FDA food grade approved silicone seal and clamps.

Physicochemical properties of the botanically derived purified CBD

[0065] The botanically derived purified CBD used in the clinical trial described in the invention comprises greater than or equal to 98% (w/w) CBD and less than or equal to 2% (w/w) of other cannabinoids. The other cannabinoids present are THC at a concentration of less than or equal to 0.1% (w/w); CBD-C1 at a concentration of less than or equal to 0.15% (w/w); CBDV at a concentration of less than or equal to 0.8% (w/w); and CBD-C4 at a concentration of less than or equal to 0.4% (w/w).

[0066] The botanically derived purified CBD used additionally comprises a mixture of both trans-THC and cis-THC. It was found that the ratio of the trans-THC to cis-THC is altered and can be controlled by the processing and purification process, ranging from 3.3:1 (trans-THC:cis-THC) in its unrefined decarboxylated state to 0.8:1 (trans-THC:cis-THC) when highly purified.

[0067] Furthermore, the cis-THC found in botanically derived purified CBD is present as a mixture of both the (+)-cis-THC and the (-)-cis-THC isoforms.

[0068] Clearly a CBD preparation could be produced synthetically by producing a composition with duplicate components.

[0069] Example 1 below describes the use of a botanically derived purified CBD in an open label, expanded-access program to investigate the clinical efficacy and safety of purified pharmaceutical cannabidiol formulation (CBD) in the treatment of patients diagnosed with Jeavon's syndrome.

EXAMPLE 1: CLINICAL EFFICACY AND SAFETY OF PURIFIED PHARMACEUTICAL CANNABIDIOL (CBD) IN THE TREATMENT OF PATIENTS DIAGNOSED WITH JEAVON'S SYNDROME.

Study design

[0070] Subjects were required to be on one or more AEDs at stable doses for a minimum of two weeks prior to baseline and to have stable vagus nerve stimulation (VNS) settings and ketogenic diet ratios for a minimum of four weeks prior to baseline.

[0071] Patients were administered botanically derived purified CBD in a 100 mg/mL sesame oil-based solution at an initial dose of between 4.4 and 20 milligrams per kilogram per day (mg/kg/day) in two divided doses. Dose was then increased weekly by 5mg/kg/day to a goal of 20 to 25 mg/kg/day.

[0072] A maximum dose of 50 mg/kg/day could be utilised for patients who were tolerating the medication but had not achieved seizure control; these patients had further weekly titration by 5mg/kg/day.

[0073] There were four patients in this study, and each received CBD for various durations of time. Modifications were made to concomitant AEDs as per clinical indication.

[0074] Seizure frequency, intensity, and duration were recorded by caregivers in a diary during a baseline period of at least 28 days. Changes in seizure frequency relative to baseline were calculated after at least 2 weeks and at defined timepoints of treatment.

Statistical Methods:

[0075] Patients may be defined as responders if they had more than 50% reduction in seizure frequency compared to baseline. The percent change in seizure frequency was calculated as follows:

$$\text{seizure frequency \% change} = \frac{(\text{weekly seizure frequency } \textit{time interval}) - (\text{weekly seizure frequency } \textit{Baseline})}{(\text{weekly seizure frequency } \textit{Baseline})}$$

[0076] The percent change of seizure frequency may be calculated for any time interval where seizure number has been recorded. For the purpose of this example the percent change of seizure frequency for the end of the treatment period was calculated as follows:

$$\text{seizure frequency \% reduction} = \frac{((\text{weekly seizure frequency } \textit{Baseline}) - (\text{weekly seizure frequency } \textit{End})) \times 100}{}$$

Results

Patient description

[0077] The four patients enrolled in the open label; expanded-access program were diagnosed with Jeavon's syndrome. These patients experienced a range of different seizure types including absence, myoclonic-absence, myoclonic and focal seizures with secondary generalisation.

[0078] The age of patients ranged from 10-39 years, all four were female as detailed in Table 1 below.

Table 1: Patient demographics, seizure type and concomitant medication

Patient Number	Age (years)	Sex	Seizure types	Concomitant AEDs
1	14.99	F	Absence	CLB
2	21.00	F	Myoclonic-absence	CLB, VPA
3	10.52	F	Myoclonic Absence Myoclonic-absence Focal with secondary generalisation	CLB, VPA, LTG
4	39.48	F	Absence	ETH, LTG, ZNS

VPA = valproic acid, CLB = clobazam, LTG = lamotrigine, ZNS = zonisamide, ETH = ethosuximide

Study medication and concomitant medications

[0079] Patients on the study were titrated up to various doses of CBD, all four patients were titrated up to at least 25 mg/kg/day.

[0080] Patients had tried an average of two AEDs prior to enrolment (range: 1-3 AEDs). Three patients were taking clobazam (CLB).

Clinical changes

[0081] Tables 2A-2D illustrate the seizure frequency for each patient as well as the dose of CBD given.

Table 2A: Seizure frequency data for Patient 1

Patient 1

Time	Seizure Type	Dose CBD (mg/kg/day)
	Absence	
Baseline	560.0	-
4 weeks	560.0	20.0
8 weeks	560.0	25.0
12 weeks	560.0	25.0
16 weeks	0	25.0
36 weeks	4.4	25.0

[0082] Patient 1 was treated for 36 weeks and experienced a 99.2% reduction in absence seizures over the treatment period.

Table 2B: Seizure frequency data for Patient 2

Patient 2		
Time	Seizure Type	Dose CBD (mg/kg/day)
	Myoclonic-absence	
Baseline	2800.0	-
4 weeks	4.0	20.0
8 weeks	0	25.0
12 weeks	0	25.0
24 weeks	0	25.0
36 weeks	120.0	25.0
48 weeks	400.0	25.0
60 weeks	400.0	25.0
72 weeks	160.0	25.0
84 weeks	200.0	24.4
108 weeks	120.0	23.9
120 weeks	1680.0	20.8
144 weeks	1000.0	17.6

[0083] Patient 2 was treated for 144 weeks and experienced a 64.3% reduction in myoclonic-absence seizures over the treatment period.

Table 2C: Seizure frequency data for Patient 3

	Patient 3				
Time	**Seizure Type**				**Dose CBD (mg/kg/day)**
	Myoclonic	**Absence**	**Myoclonic-absence**	**Focal with secondary generalisation**	
Baseline	489.0	11.0	1257.0	4.0	-
8 weeks	0	0	156.0	0	4.4
12 weeks	0	0	29.0	0	4.4
16 weeks	0	0	16.0	0	5.0
24 weeks	1163.0	0	0	0	6.0
36 weeks	807.0	0	0	0	6.0
48 weeks	0	0	426.0	0	8.0
60 weeks	183.0	0	0	0	8.0
72 weeks	1452.0	0	0	4.0	25.1
84 weeks	2784.0	4.0	0	0	30.0
96 weeks	998.0	3.0	0	0	27.9
120 weeks	1579.0	0	0	0	27.9
132 weeks	1066.0	14.0	0	0	23.5
144 weeks	1871.0	0	0	0	23.5

[0084] Patient 3 was treated for 144 weeks and experienced a 100% reduction in absence seizures, myoclonic-absence seizures and focal seizures with secondary generalisation over the treatment period.

Table 2D: Seizure frequency data for Patient 4

Patient 4		
Time	**Seizure Type**	**Dose CBD (mg/kg/day)**
	Absence	
Baseline	247.4	-
4 weeks	420.0	15.0

8 weeks	376.0	20.0
16 weeks	309.0	30.0
24 weeks	192.0	25.0
36 weeks	120.0	25.0
48 weeks	133.5	25.0
60 weeks	129.8	25.0
72 weeks	113.2	25.0
84 weeks	98.0	25.0

[0085] Patient 4 was treated for 84 weeks and experienced a 60.4% reduction in absence seizures over the treatment period.

[0086] Overall, patients reported reductions of 60.4-100.0% in seizures over period of treatment with CBD.

[0087] CBD was effective in reducing the frequency of the following seizure types: absence, myoclonic-absence and focal seizures with impairment. Significantly, one patient became seizure free of absence seizures, myoclonic-absence seizures and focal seizures with secondary generalisation after 144 weeks (patients #3) of CBD treatment.

Conclusions

[0088] These data indicate that CBD was able to significantly reduce the number of seizures associated with Jeavon's syndrome. Clearly the treatment is of significant benefit in this difficult to treat epilepsy syndrome given the high responder rate experienced in many of the patients.

[0089] Of interest is that patients with absence seizures (patients #1, 3 and 4) obtained significant benefit.

[0090] In conclusion, this study signifies the use of CBD for treatment of seizures associated with Jeavon's syndrome. Seizure types include absence, myoclonic-absence and focal seizures with secondary generalisation for which seizure frequency rates decreased by significant rates, by 60.4-100.0%.

References

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CLAIMS

1. A cannabidiol (CBD) preparation for use in the treatment of seizures associated with Jeavon's syndrome, wherein the CBD preparation comprises greater than or equal to 98% (w/w) CBD and less than or equal to 2% (w/w) other cannabinoids, wherein the less than or equal to 2% (w/w) other cannabinoids comprise the cannabinoids tetrahydrocannabinol (THC); cannabidiol-C1 (CBD-C1); cannabidivarin (CBDV); and cannabidiol-C4 (CBD-C4), and wherein the THC is present as a mixture of trans-THC and cis-THC.

2. A CBD preparation for use according to claim 1, wherein the seizures associated with Jeavon's syndrome are absence, myoclonic-absence, myoclonic and focal seizures with secondary generalisation.

3. A CBD preparation to any of the preceding claims, wherein the CBD preparation is used in combination with one or more concomitant anti-epileptic drugs (AED).

4. A CBD preparation for use according to claim 3, wherein the one or more AED is selected from the group consisting of: valproic acid, clobazam, lamotrigine, zonisamide and ethosuximide.

5. A CBD preparation for use according to any of the preceding claims, wherein the CBD is present is isolated from cannabis plant material.

6. A CBD preparation for use according to any of the preceding claims, wherein at least a portion of at least one of the cannabinoids present in the CBD preparation is isolated from cannabis plant material.

7. A CBD preparation for use according to claims 1 to 4, wherein the CBD is present as a synthetic preparation.

8. A CBD preparation for use according to claim 7, wherein at least a portion of at least one of the cannabinoids present in the CBD preparation is prepared synthetically.

9. A CBD preparation for use according to any of the preceding claims, wherein the dose of CBD is greater than 5 mg/kg/day.

10. A CBD preparation for use according to any of the preceding claims, wherein the dose of CBD is 20 mg/kg/day.

11. A CBD preparation for use according to any of the preceding claims, wherein the dose of CBD is 25 mg/kg/day.

12. A CBD preparation for use according to any of the preceding claims, wherein the dose of CBD is 50 mg/kg/day.

13. A method of treating seizures associated with Jeavon's syndrome comprising administering a cannabidiol (CBD) preparation to the subject in need thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/069858

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/05 A61K31/19 A61K31/4015 A61K31/423 A61K31/53
A61K31/551 A61P25/08
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KUCHENBUCH MATHIEU ET AL: "Add-on cannabidiol significantly decreases seizures in 3 patients with SYNGAP1 developmental and epileptic encephalopathy", EPILEPSIA OPEN, vol. 5, no. 3, 4 June 2020 (2020-06-04), pages 496-500, XP055847803, ISSN: 2470-9239, DOI: 10.1002/epi4.12411 Retrieved from the Internet: URL:https://onlinelibrary.wiley.com/doi/full-xml/10.1002/epi4.12411>	13
Y	the whole document -----	1-12
Y	WO 2015/193668 A1 (GW PHARMA LTD [GB]) 23 December 2015 (2015-12-23) paragraphs [0019], [0020], [0043], [0045]; claims 1,4 -----	1-13
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 October 2021	08/11/2021

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/069858

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 2 539 472 A (GW RES LTD [GB]) 21 December 2016 (2016-12-21) claims 1,5 -----	1-13
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PCT/EP2021/069858

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