(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 January 2022 (27.01.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/017909 A1

(51) International Patent Classification:

A61K 31/05 (2006.01)	*A61K 31/4192* (2006.01)
A61K 31/19 (2006.01)	*A61K 31/165* (2006.01)
A61K 31/4015 (2006.01)	*A61K 31/53* (2006.01)
A61K 31/551 (2006.01)	*A61K 31/7048* (2006.01)
A61K 31/197 (2006.01)	*A61K 45/06* (2006.01)
A61K 31/423 (2006.01)	*A61P 25/08* (2006.01)

(21) International Application Number:
PCT/EP2021/069782

(22) International Filing Date:
15 July 2021 (15.07.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2011120.9 20 July 2020 (20.07.2020) GB

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) **Title:** USE OF CANNABIDIOL IN THE TREATMENT OF SEIZURES ASSOCIATED WITH RARE EPILEPSY SYNDROMES RELATED TO STRUCTURAL ABNORMALITIES OF THE BRAIN

(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 experienced in patients diagnosed with Cortical Dysplasia and Cortical Brain Malformation. In a further embodiment the types of seizures include atonic, tonic, and focal without impairment seizures. Preferably the dose of CBD is between 5 mg/kg/day to 50 mg/kg/day.

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USE OF CANNABIDIOL IN THE TREATMENT OF SEIZURES ASSOCIATED WITH RARE EPILEPSY SYNDROMES RELATED TO STRUCTURAL ABNORMALITIES OF THE BRAIN

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 experienced in patients diagnosed with Cortical Dysplasia and Cortical Brain Malformation. In a further embodiment the types of seizures include atonic, tonic, and focal without impairment seizures. 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] Cortical brain malformation, also known as Malformations of Cortical Development (MCD), is the most common cause of medically refractory epilepsy in the pediatric population and the second/third most common etiology of medically intractable seizures in adults[1]. MCD encompass a wide spectrum of disorders with various underlying genetic etiologies and clinical manifestations. They are brain malformations that result from abnormalities affecting the normal processes of cortical development and involve cells that under normal circumstances would participate in formation of the cerebral cortex[2]. They are often associated with recurrent seizures which are difficult to control and arise as a consequence of either malpositioning of normal cortical neurons or the presence of abnormal cortical neurons.

[0016] Cortical dysplasia is a malformation of cortical development. Both genetic and acquired factors are involved in the pathogenesis of cortical dysplasia.

[0017] In general, three types of cortical dysplasia are recognized[1]. Type I focal cortical dysplasia with mild symptomatic expression and late onset, is more often seen in adults, with changes present in the temporal lobe. Clinical symptoms are more severe in type II of cortical dysplasia usually seen in children. In this type, more extensive changes occur outside the temporal lobe with predilection for the frontal lobes. Type III includes one of the above-described dysplasias with damage in another part of the brain e.g. hippocampal sclerosis, tumor, vascular malformation or acquired pathology during early life.

[0018] Anticonvulsants are a first line treatment in cortical dysplasia. If anticonvulsants fail to control seizure activity, neurosurgery may be required to remove or disconnect the abnormal cells from the rest of the brain. Neurosurgery can range from removing an entire hemisphere, a small lesionectomy, or multiple transsections to try to disconnect the abnormal tissue from the rest of the brain.

[0019] 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.

[0020] 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.

[0021] In 2019 a Scottish newspaper reported the treatment of a child with cortical dysplasia using CBD medication[3]. There is no mention of the types of seizures experienced by the patient.

[0022] García-Rincón *et al.* (2019)[4] attempted to characterize the possible contribution of endocannabinoid system signaling to focal cortical dysplasia. They found that an altered endocannabinoid system contributes to increased activity of a protein signaling pathway, the

mammalian target of rapamycin complex 1 (mTORC1) pathway, which is itself associated with some malformations of cortical development such as focal cortical dysplasia.

[0023] Szaflarski et al. (2018)[5] and Laux et al. (2019)[6] disclose the use of CBD to treat epileptic syndromes including Lennox-Gastaut Syndrome and Dravet Syndrome. Cortical malformation and dysplasia are listed in a list of several etiologies included in the patient cohort. However, it is not disclosed what types of seizures these patients experienced and indeed whether treatment was effective in reducing their seizures.

[0024] Crippa et al (2016)[7] discloses the use of a cannabinoid treatment containing no THC to treat a girl with focal cortical dysplasia. There is no mention of the types of seizures experienced by the patient. Further disclosures in the form of news articles[8,9] refer to a patient with cortical dysplasia treated with CBD. Again, there is no disclosure of seizure types suffered by the patient.

[0025] The applicant has found by way of an open label, expanded-access program that treatment with CBD resulted in a significant reduction in atonic, tonic and focal without impairment seizures in patients with Cortical Dysplasia and Cortical Brain Malformation.

BRIEF SUMMARY OF THE DISCLOSURE

[0026] 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 Cortical Dysplasia and Cortical Brain Malformation.

[0027] In a further embodiment the seizures associated with Cortical Dysplasia and Cortical Brain Malformation are atonic, tonic and focal without impairment seizures.

[0028] In a further embodiment, the CBD preparation comprises greater than 95% (w/w) CBD and not more than 0.15% (w/w) tetrahydrocannabinol (THC).

[0029] 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.

[0030] Preferably the CBD preparation is used in combination with one or more concomitant anti-epileptic drugs (AED).

[0031] Preferably the one or more AED is selected from the group consisting of: valproic acid, levetiracetam, clobazam, vigabatrin, zonisamide, rufinamide, lacosamide, topiramate and lamotrigine. More preferably the AED is clobazam.

[0032] 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.

[0033] 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.

[0034] 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.

[0035] In accordance with a second aspect of the present invention there is provided a method of treating seizures associated with Cortical Dysplasia and Cortical Brain Malformation comprising administering a cannabidiol (CBD) preparation to the subject in need thereof.

DEFINITIONS

[0036] Definitions of some of the terms used to describe the invention are detailed below:

[0037] 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).

[0038] "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.

[0039] "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.

[0040] "Synthetic cannabinoids" are compounds that have a cannabinoid or cannabinoid-like structure and are manufactured using chemical means rather than by the plant.

[0041] 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.

[0042] "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.

[0043] "Atonic seizures" occur when a person suddenly loses muscle tone so their head or body may go limp. They are also known as drop attacks. In some children, only their head drops suddenly. They can begin in one area or side of the brain (focal onset) or both sides of the brain (generalized onset).

[0044] "Tonic seizures" can be generalised onset, affecting both sides of the brain, or they can be focal onset, starting in just one side of the brain. If a tonic seizure starts in both sides of the brain, all muscles tighten and the subject's body goes stiff. If standing, they may fall to the floor, their neck may extend, eyes open wide and roll upwards, whilst their arms may raise upwards and legs stretch or contract. If a tonic seizure starts in one side of the brain muscles tighten in just one area of the body. Tonic seizures usually last less than one minute.

[0045] "Focal seizures without impairment" are seizures which originate within networks limited to only one hemisphere where the awareness or responsiveness of the subject is not impaired.

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.	NMT 10^7cfu/g NMT 10^5cfu/g NMT 10^2cfu/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 Cortical Dysplasia and Cortical Brain Malformation.

EXAMPLE 1: CLINICAL EFFICACY AND SAFETY OF PURIFIED PHARMACEUTICAL CANNABIDIOL (CBD) IN THE TREATMENT OF CORTICAL DYSPLASIA AND CORTICAL BRAIN MALFORMATION

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 five 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 9 patients in this study, and each received CBD for at least 3 months. 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. he percent change in seizure frequency was calculated as follows:

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

[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:

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

Results

Patient description

[0077] The 8 patients enrolled in the open label, expanded-access program were diagnosed with Cortical Dysplasia and Cortical Brain Malformation. These patients experienced several different seizure types including atonic, tonic and focal seizures without impairment and were taking several concomitant AEDs.

[0078] The age of patients ranged from 4-16 years, five were male and three 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	15.53	F	Tonic-clonic, atonic	VPA, CLP, DZP, PMP
2	4.45	M	tonic	RFN, CLN, PHB
3	12.00	M	Tonic, atonic, myoclonic	CLB, LEV
4	5.00	M	Tonic	LTG, OXC, VGB
5	4.00	F	Tonic	TPM, OXC, LCS
6	16.18	M	Focal without impairment	LEV, CLN, OXC, PMP
7	12.36	F	Focal without impairment, focal with impairment	TPM
8	12.90	M	Tonic, atonic	CLB, ETH, OXC

VPA = valproic acid, LEV = levetiracetam, CLB = clobazam, VGB = vigabatrin, ZNS = zonisamide, RFN = rufinamide, LCS = lacosamide, TPM = topiramate, LTG = lamotrigine, ETH= Ethosuximide, OXC = Oxcarbarmazepine, CLR = Clorazepate, DZP = Diazepam, PMP = Perampanel, CLN = Clonazepam, PHB = Phenobarbital

Study medication and concomitant medications

[0079] All eight patients were titrated up to at least 5 mg/kg/day of CBD, seven patients were titrated up to at least 25 mg/kg/day (#1, 3-8), and two patients were titrated up to 50 mg/kg/day (#4, 5).

[0080] The average number of concomitant AEDs at the time of starting CBD was three per patient (range: 1-4, median: 3).

Clinical changes

[0081] The average baseline was 81.8 seizures per week (range: 2.0-280.0 seizures per week median: 24 seizures per week). Tables 2A-H 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)**
	Tonic-clonic	**Atonic**	
Baseline	13.0	2.0	-
2 weeks	12.0	0.0	10.0
4 weeks	25.0	1.0	20.0
8 weeks	17.0	3.0	25.0
12 weeks	16.0	1.0	25.0

[0082] Patient 1 was treated for 12 weeks and experienced a 50% reduction in atonic seizures over the treatment period.

Table 2B: Seizure frequency data for Patient 2

Patient 2		
Time	**Seizure Type**	**Dose CBD (mg/kg/day)**
	Tonic	
Baseline	140.0	-
12 weeks	70.0	5.0

[0083] Patient 2 was treated for 12 weeks and experienced a 50% reduction in tonic seizures over the treatment period.

Table 2C: Seizure frequency data for Patient 3

Patient 3				
Time	Seizure Type			Dose CBD (mg/kg/day)
	Tonic	Atonic	Myoclonic	
Baseline	20.0	24.0	4.0	-
4 weeks	4.0	0.0	0.0	20.0
8 weeks	200.0	0.0	0.0	25.0
12 weeks	140.0	12.0	56.0	14.8
24 weeks	140.0	12.0	28.0	9.7
36 weeks	60.0	16.0	0.0	10.9
48 weeks	40.0	8.0	20.0	10.6
60 weeks	28.0	1.0	1.0	17.1
72 weeks	40.0	1.0	1.0	16.2
96 weeks	28.0	2.0	16.0	24.5
120 weeks	6.0	4.0	16.0	17.7
132 weeks	6.0	4.0	16.0	17.3
144 weeks	56.0	2.0	40.0	19.9

[0084] Patient 3 was treated for 144 weeks and experienced a 91.7% reduction in atonic seizures over the treatment period.

Table 2D: Seizure frequency data for Patient 4

Patient 4		
Time	Seizure Type	Dose CBD (mg/kg/day)
	Tonic	
Baseline	196.0	-

4 weeks	60.0	20.0
8 weeks	40.0	25.0
12 weeks	80.0	30.0
24 weeks	24.0	50.0
36 weeks	32.0	50.0
48 weeks	54.0	50.0
60 weeks	24.0	50.0
72 weeks	24.0	49.0
84 weeks	36.0	46.0
96 weeks	22.0	50.0
120 weeks	16.0	42.6
132 weeks	36.0	49.8

[0085] Patient 4 was treated for 132 weeks and experienced an 81.6% reduction in tonic seizures over the treatment period.

Table 2E: Seizure frequency data for Patient 5

Patient 5		
Time	**Seizure Type**	**Dose CBD (mg/kg/day)**
	Tonic	
Baseline	4.0	-
4 weeks	3.2	20.0
8 weeks	11.0	35.0
12 weeks	1.0	50.0
24 weeks	0.0	50.0
36 weeks	0.0	47.0
48 weeks	1.0	46.0
60 weeks	1.0	49.0
72 weeks	0.0	50.0
84 weeks	0.0	50.0
96 weeks	0.0	49.7

108 weeks	0.0	49.7
132 weeks	0.0	49.1
144 weeks	0.0	50.0

[0086] Patient 5 was treated for 144 weeks and experienced a 100% reduction in tonic seizures over the treatment period.

Table 2F: Seizure frequency data for Patient 6

Patient 6		
Time	**Seizure Type**	**Dose CBD (mg/kg/day)**
	Focal without impairment	
Baseline	20.0	-
4 weeks	8.0	25.0
8 weeks	0.0	25.0
16 weeks	4.0	25.0
24 weeks	2.0	25.0

[0087] Patient 6 was treated for 24 weeks and experienced a 90% reduction in focal seizures without impairment over the treatment period.

Table 2G: Seizure frequency data for Patient 7

Patient 7			
Time	**Seizure Type**		**Dose CBD (mg/kg/day)**
	Focal without impairment	**Focal with impairment**	
Baseline	233.0	49.0	-
2 weeks	182.0	22.0	10.0
4 weeks	62.0	26.0	20.0
8 weeks	125.0	35.0	25.0
12 weeks	112.0	40.0	25.0

16 weeks	93.3	66.7	25.0
24 weeks	96.8	62.4	25.0
36 weeks	39.7	94.8	20.0
48 weeks	92.9	62.5	20.0
60 weeks	141.2	72.8	20.0
72 weeks	139.4	179.7	20.0

[0088] Patient 7 was treated for 72 weeks and experienced a 40.2% reduction in focal seizures without impairment over the treatment period.

Table 2H: Seizure frequency data for Patient 8

Patient 8			
Time	**Seizure Type**		**Dose CBD (mg/kg/day)**
	Tonic	**Atonic**	
Baseline	280.0	80.0	-
4 weeks	6.0	-	20.0
8 weeks	5.0	-	25.0
12 weeks	60.0	12.0	25.0
16 weeks	56.0	24.0	25.0
24 weeks	32.0	4.0	25.0
36 weeks	896.0	4.0	10.0

[0089] Patient 8 was treated for 36 weeks and experienced a 95.0% reduction in atonic seizures over the treatment period.

[0090] Overall, patients reported reductions of 40.2-100.0% in seizures over period of treatment with CBD.

[0091] CBD was effective in reducing the frequency of the following seizure types: atonic, tonic and focal without impairment. Significantly, one patient became seizure free of tonic seizures after 12 months of CBD treatment.

Conclusions

[0092] These data indicate that CBD was able to significantly reduce the number of seizures associated with Cortical Dysplasia and Cortical Brain Malformation. Clearly the treatment is of significant benefit in this difficult to treat epilepsy syndrome given the high response rate experienced in all patients.

[0093] Of interest is that a patient with tonic seizures (patient 5) obtained significant benefit whereby the patient was completely seizure free after 12 months of treatment.

[0094] In conclusion, this study signifies the use of CBD for treatment of seizures associated with Cortical Dysplasia and Cortical Brain Malformation. Seizure types include atonic, tonic, and focal seizures without impairment for which seizure frequency rates decreased by significant rates, by 40.2-100.0%.

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CLAIMS

1. A cannabidiol (CBD) preparation for use in the treatment of seizures associated with Cortical Dysplasia and Cortical Brain Malformation, wherein the seizures associated with Cortical Dysplasia and Cortical Brain Malformation are atonic, tonic, and focal without impairment seizures.

2. A CBD preparation for use according to any of the preceding claims, wherein the CBD preparation comprises greater than 95% (w/w) CBD and not more than 0.15% (w/w) tetrahydrocannabinol (THC).

3. A CBD preparation for use according to any of the preceding claims, 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.

4. 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).

5. A CBD preparation for use according to claim 4, wherein the one or more AED is selected from the group consisting of: valproic acid, levetiracetam, clobazam, vigabatrin, zonisamide, rufinamide, lacosamide, topiramate and lamotrigine.

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

7. 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.

8. A CBD preparation for use according to claims 1 to 5, wherein the CBD is present as a synthetic preparation.

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

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

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

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

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

14. A method of treating seizures associated with Cortical Dysplasia and Cortical Brain Malformation comprising administering a cannabidiol (CBD) preparation to the subject in need thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/069782

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/05 A61K31/19 A61K31/4015 A61K31/551 A61K31/197
A61K31/423 A61K31/4192 A61K31/165 A61K31/53 A61K31/7048
A61K45/06 A61P25/08

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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CARABALLO ROBERTO ET AL: "Effectiveness of cannabidiol in a prospective cohort of children with drug-resistant epileptic encephalopathy in Argentina", SEIZURE, BAILLIERE TINDALL, LONDON, GB, vol. 80, 6 June 2020 (2020-06-06), pages 75-80, XP086246226, ISSN: 1059-1311, DOI: 10.1016/J.SEIZURE.2020.06.005 [retrieved on 2020-06-06]	14
Y	abstract page 76, paragraph 2.2 tables 1, 3	1-14
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
26 October 2021	05/11/2021

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SULAK DUSTIN ET AL: "The current status of artisanal cannabis for the treatment of epilepsy in the United States", EPILEPSY AND BEHAVIOR, ACADEMIC PRESS, SAN DIEGO, CA, US, vol. 70, 21 February 2017 (2017-02-21), pages 328-333, XP085033470, ISSN: 1525-5050, DOI: 10.1016/J.YEBEH.2016.12.032	14
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Y	page 176, right-hand column, line 47 - line 54	1-14
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Y	page 2, right-hand column, line 8 - page 3, left-hand column, line 15	1-14

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SZAFLARSKI JERZY P. ET AL: "Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: Expanded access program results", EPILEPSIA, vol. 59, no. 8, 1 August 2018 (2018-08-01) , pages 1540-1548, XP055832712, New York , US ISSN: 0013-9580, DOI: 10.1111/epi.14477 Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6175436/pdf/EPI-59-1540.pdf> abstract page 1541, paragraph 2.2 - page 1542 table 1 figure 2	1-14
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/EP2021/069782

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