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(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 those which are experienced in patients diagnosed with craniosynostosis. In a further embodiment the types of seizures include 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.

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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 those which are experienced in patients diagnosed with craniosynostosis. In a further embodiment the types of seizures include 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] Craniosynostosis occurs when one or more of the joints that connect the bones of a baby's skull (cranial sutures) close prematurely, before brain growth is complete.

[0016] Symptoms and severity vary depending on how many sutures close prematurely. Most commonly, only one closes prematurely and in such cases, brain growth may continue in other parts of the skull, leading only to an abnormally-shaped skull and no other health problems or complications. On the other hand, if multiple sutures close prematurely, brain growth can be restricted, which can lead to increased pressure in the skull, impaired brain development, seizures, blindness, and intellectual disability.

[0017] Most cases of isolated craniosynostosis occur sporadically and have no known cause. In some cases, isolated craniosynostosis is due to a mutation in any of several genes, with autosomal dominant inheritance. When craniosynostosis is a feature of a larger syndrome, the cause and inheritance pattern depend on the syndrome the person has.

[0018] The long-term outlook depends on how many sutures are involved and whether the child has a larger syndrome or other health problems.

[0019] Treatment for craniosynostosis depends on the severity in each child and may involve surgery in infancy to relieve pressure within the skull, allow for brain growth, and improve the appearance of the shape of the head.

[0020] 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.

[0021] 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.

[0022] Applicant's previous applications such as WO 2019/145700, WO 2015/193668 and WO 2016/203239 disclose the effectiveness of highly purified CBD in the treatment of various epileptic syndromes. None provide any data of patients diagnosed with craniosynostosis.

[0023] The applicant has found by way of an open label, expanded-access program that treatment with CBD resulted in a significant reduction in focal seizures without impairment and focal seizures with secondary generalisation in patients with craniosynostosis.

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 craniosynostosis.

[0025] In a further embodiment, the seizures associated with craniosynostosis are 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: levetiracetam, lacosamide and topiramate.

[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 craniosynostosis 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] "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.

[0042] "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.

[0043] "Focal seizure with secondary generalisation" 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

[0044] The following describes the production of the highly-purified (>95% w/w) cannabidiol extract which has a known and constant composition.

[0045] 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 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

[0046] 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.

[0047] 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.

[0048] 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).

[0049] 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.

[0050] 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

[0051] 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.

[0052] 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.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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

[0057] 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

[0058] 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.

[0059] Decarboxylation of CBDA to CBD was carried out using heat. BRM was decarboxylated at 115ºC for 60 minutes.

[0060] 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

[0061] 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

[0062] 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

[0063] 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).

[0064] 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.

[0065] 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.

[0066] Clearly a CBD preparation could be produced synthetically by producing a composition with duplicate components.

[0067] 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 craniosynostosis.

EXAMPLE 1: CLINICAL EFFICACY AND SAFETY OF PURIFIED PHARMACEUTICAL CANNABIDIOL (CBD) IN THE TREATMENT OF PATIENTS DIAGNOSED WITH CRANIOSYNOSTOSIS

Study design

[0068] The subject was 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.

[0069] The patient was administered botanically derived purified CBD in a 100 mg/mL sesame oil-based solution at an initial dose of 10 milligrams per kilogram per day (mg/kg/day) in two divided doses. Dose was then increased weekly by 5-10mg/kg/day to a goal of 25 mg/kg/day.

[0070] A maximum dose of 50 mg/kg/day could be utilised if the patient was tolerating the medication but had not achieved seizure control; the patient had further weekly titration by 5mg/kg/day.

[0071] There was one patient in this study, and they received CBD for 16 weeks. Modifications were made to concomitant AEDs as per clinical indication.

[0072] 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:

[0073] 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:

$$\text{seizure frequency \% change} = \frac{(\text{weekly seizure frequency } \textit{time interval}) - (\text{weekly seizure frequency } \textit{Baseline})}{(\text{weekly seizure frequency } \textit{Baseline})} \times 100$$

[0074] 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:

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

Results

Patient description

[0075] The one patient enrolled in the open label, expanded-access program was diagnosed with craniosynostosis. The patient experienced several different seizure types including focal seizures without impairment and focal seizures with secondary generalisation and was taking several concomitant AEDs.

[0076] The patient was 9 years old and she was 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	9.42	F	Focal without impairment, focal with secondary generalisation	LEV, TPM, LCS

LEV = levetiracetam, LCS = lacosamide, TPM = topiramate

Study medication and concomitant medications

[0077] The patient on the study was titrated up to 25 mg/kg/day of CBD. The patient was on three concomitant AEDs at the time of starting CBD.

Clinical changes

[0078] Tables 2 illustrates the seizure frequency for the patient as well as the dose of CBD given.

Table 2: Seizure frequency data for Patient 1

Patient 1			
Time	**Seizure Type**		**Dose CBD (mg/kg/day)**
	Focal without impairment	**Focal with secondary generalisation**	
Baseline	14.0	66.0	-
2 weeks	16.0	54.0	10.0
4 weeks	11.2	31.6	20.0
8 weeks	7.7	29.0	25.0

12 weeks	11.0	31.0	25.0
16 weeks	13.0	35.0	25.0

[0079] Patient 1 was treated for 16 weeks and experienced a 7.1% reduction in focal seizures without impairment and a 47.0% reduction in focal seizures with secondary generalisation over the treatment period.

[0080] Overall, the patient reported reductions of 7.1-47.0% in seizures over period of treatment with CBD. CBD was effective in reducing the frequency of focal seizures without impairment and focal seizures with secondary generalisation.

Conclusions

[0081] These data indicate that CBD was able to significantly reduce the number of seizures associated with craniosynostosis. Clearly the treatment is of significant benefit in this difficult to treat epilepsy syndrome given the high response rate experienced in the patient.

[0082] In conclusion, this study signifies the use of CBD for treatment of seizures associated with craniosynostosis. Seizure types include focal seizures without impairment and focal seizures with secondary generalisation for which seizure frequency rates decreased, by up to 47%.

CLAIMS

1. A cannabidiol (CBD) preparation for use in the treatment of seizures associated with craniosynostosis.

2. A CBD preparation for use according to claim 1, wherein the seizures associated with craniosynostosis are focal seizures without impairment and focal seizures with secondary generalisation.

3. 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).

4. 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.

5. 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).

6. A CBD preparation for use according to claim 5, wherein the one or more AED is selected from the group consisting of: levetiracetam, lacosamide and topiramate.

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

8. 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.

9. A CBD preparation for use according to claims 1 to 6, wherein the CBD is present as a synthetic preparation.

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

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

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

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

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

15. A method of treating seizures associated with craniosynostosis comprising administering a cannabidiol (CBD) preparation to the subject in need thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/069893

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/05 A61K31/4015 A61K31/4192 A61P25/08 A61K31/7048 A61K45/06
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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/207319 A1 (GW RES LTD [GB]) 31 October 2019 (2019-10-31) par. 207; example 9; claims 4, 7, 43 -----	1-15
X	GB 2 531 282 A (GW PHARMA LTD [GB]) 20 April 2016 (2016-04-20) par. 3; table 1; example 1; claims -----	1-15

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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

"E" earlier application or patent but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"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
28 October 2021	05/11/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Scheithe, Rupert

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/069893

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DEVINSKY ORRIN ET AL: "Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial", LANCET NEUROLOGY, LANCET PUBLISHING GROUP, LONDON, GB, vol. 15, no. 3, 24 December 2015 (2015-12-24), pages 270-278, XP029415431, ISSN: 1474-4422, DOI: 10.1016/S1474-4422(15)00379-8 whole document, particularly summary; chapter "Procedures"; table 2	1-15

X	WO 2016/203239 A1 (GW RES LTD [GB]) 22 December 2016 (2016-12-22)	1-15
Y	example 1	2

Y	RUSSO ETHAN B ED - BENBADIS SELIM R: "Cannabis and epilepsy: An ancient treatment returns to the fore", EPILEPSY AND BEHAVIOR, ACADEMIC PRESS, SAN DIEGO, CA, US, vol. 70, 15 December 2016 (2016-12-15), pages 292-297, XP085033469, ISSN: 1525-5050, DOI: 10.1016/J.YEBEH.2016.09.040 chapter 2.2.3.	2

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2021/069893

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2019207319 A1	31-10-2019	AU 2019259230 A1	26-11-2020
		BR 112020021884 A2	26-01-2021
		CA 3097665 A1	31-10-2019
		CN 112512585 A	16-03-2021
		EA 202092582 A1	17-02-2021
		EP 3784283 A1	03-03-2021
		GB 2574321 A	04-12-2019
		JP 2021522261 A	30-08-2021
		KR 20210005128 A	13-01-2021
		US 2021015789 A1	21-01-2021
		US 2021052512 A1	25-02-2021
		WO 2019207319 A1	31-10-2019
GB 2531282 A	20-04-2016	AU 2015332212 A1	20-04-2017
		AU 2021204353 A1	22-07-2021
		BR 112017007777 A2	16-01-2018
		CA 2963208 A1	21-04-2016
		DK 3206716 T3	17-08-2020
		EP 3206716 A1	23-08-2017
		EP 3735964 A1	11-11-2020
		ES 2811327 T3	11-03-2021
		GB 2531282 A	20-04-2016
		HR P20201230 T1	05-02-2021
		HU E053262 T2	28-06-2021
		IL 251529 A	29-04-2021
		JP 6656241 B2	04-03-2020
		JP 2017531667 A	26-10-2017
		JP 2020073580 A	14-05-2020
		LT 3206716 T	26-10-2020
		PL 3206716 T3	28-12-2020
		PT 3206716 T	17-08-2020
		SI 3206716 T1	30-10-2020
		US 2016166515 A1	16-06-2016
		US 2017172941 A1	22-06-2017
		US 2017266126 A1	21-09-2017
		US 2019091171 A1	28-03-2019
		US 2020000741 A1	02-01-2020
		US 2020069608 A1	05-03-2020
		US 2020323792 A1	15-10-2020
		US 2021196651 A1	01-07-2021
		US 2021244685 A1	12-08-2021
		WO 2016059403 A1	21-04-2016
WO 2016203239 A1	22-12-2016	AU 2016278088 A1	18-01-2018
		CA 2989779 A1	22-12-2016
		EP 3310390 A1	25-04-2018
		GB 2539472 A	21-12-2016
		HK 1253580 A1	21-06-2019
		JP 2018521042 A	02-08-2018
		US 2017007551 A1	12-01-2017
		US 2020297656 A1	24-09-2020
		WO 2016203239 A1	22-12-2016