National Institute for Health Research

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Cannabidiol in a pharmaceutical formulation (Epidiolex; GWP42003-P) for Lennox-Gastaut syndrome in children and adults

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LAY SUMMARY

Lennox-Gastaut syndrome is a rare and severe form of epilepsy that is most commonly found in children. It is characterised by slow mental development and various types of seizures that are difficult to treat. The condition is five times more common in males than females and generally when patients reach adulthood, the severity of the disease lessens.

A pharmaceutical formulation of the cannabis extract, cannabidiol is being developed for those patients who do not respond to previous treatments for seizures associated with Lennox-Gastaut syndrome. This is taken as an oral solution.

TARGET GROUP

Lennox-Gastaut syndrome: uncontrolled; children and young adults – second and subsequent line.

TECHNOLOGY

DESCRIPTION

Cannabidiol (Epidiolex; GWP42003-P) is a small-molecule cannabinoid compound extracted from the Cannabis sativa plant, which is currently being developed for the adjunctive treatment of Lennox-Gastaut syndrome in patients inadequately controlled by current anti-epileptic drugs. The precise mechanism by which cannabidiol exerts its anti-convulsant effects in humans is unknown, however it does reduce neuronal hyperexcitability through modulation of intracellular calcium, via GPR55 receptors and TRPV1 channels and modulation of adenosine-mediated signalling.

In the two completed phase III studies, cannabidiol was given as an oral solution containing 100mg/mL of the active substance for a 2 week period during which the dose was titrated to 20mg/kg/day in two equally divided doses, followed by 12 weeks of maintenance therapy.[1, 2]

Cannabidiol is in phase III development for the following indications[2]:

- Lennox-Gastaut syndrome
- Dravet syndrome
- Tuberous Sclerosis
- Infantile spasms

Cannabidiol does not currently have a Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

The current treatments for paediatric epilepsy sub-indications, such as Dravet syndrome and Lennox-Gastaut syndrome, remain suboptimal. Many subjects remain uncontrolled despite treatment and many experience major side effects. Cannabidiol, as an add-on therapy to existing treatment, provides evidence of additional efficacy. This in addition to side effects reported as mostly mild or moderate mean cannabidiol could be an important addition to current treatment options. Furthermore, as most patients tend to be refractory to the current treatment options, cannabidiol represents a potential novel and innovative solution with positive findings in clinical studies thus far.[1]

DEVELOPER

GW Research Ltd.

AVAILABILITY, LAUNCH or MARKETING

Cannabidiol is a designated orphan drug in the EU and USA for Lennox-Gastaut syndrome.[2]

PATIENT GROUP

BACKGROUND

Lennox-Gastaut syndrome is a severely debilitating form of generalised paediatric epilepsy that begins in early childhood between the ages of 2 and 7 years.[3,4] The condition is characterised by slow mental development, diffuse slow interictal spike wave in the waking electroencephalogram (< 3 Hz), fast rhythmic burst (10 Hz) during sleep, and several types of epileptic seizures.[4] These seizure types include tonic seizures (muscle contraction lasting few seconds to minutes), atypical absence seizures (during which the person has a blank stare but is still partly aware of their surroundings) and drop seizures (brief loss of muscle tone and consciousness, causing abrupt falls).[3] Tonic seizures are considered the most common of all, and are prerequisite in the diagnosis of the condition, whilst atypical absence seizures are the second most common type of seizures experienced.[5] Behavioural disorders are further associated with the condition; these include aggressiveness and hyperactivity as well as some forms of learning disability and personality disorder.[3]

Lennox-Gastaut syndrome can be defined as either cryptogenic, which appears without any antecedent history or brain pathology evidence, or symptomatic, which is associated with pre-existing brain damage such as perinatal asphyxia, tuberous sclerosis, meningoencephalitis sequelae, cortical dysplasia, cranial trauma, and more rarely tumours or metabolic diseases.[4] Cryptogenic cases tend to have a later onset than symptomatic cases and account for up to 30% of those with Lennox-Gastaut syndrome.[6,7] As these cases have an unknown origin of disease, seizures associated with Lennox-Gastaut syndrome are generally considered one of the most refractory of all epileptic encephalopathies to current treatment options.[6,8]

As seizures can persist into adulthood, the concerns for social integration and appropriate care make the condition one of the most complex epileptic disorders to manage for both specialists in epilepsy and neurologists.[5] Despite reported incidence of Lennox-Gastaut being rare in adolescence, patients are rarely relieved of seizures, and over time, mental and psychiatric conditions become worse and can disturb a patient's quality of life.[9,10] As patients age, 33% with cryptogenic Lennox-Gastaut syndrome and 55% of symptomatic cases lose the characteristic features of the condition,[11] whilst 30-50% maintain the slow spike-wave pattern and clinical characteristics through their 20s.[12] Throughout adulthood, seizures may persist with reduced frequency, for example daytime tonic and atonic seizures can decrease or disappear, therefore adults with Lennox-Gastaut do not experience the same level of falls compared to younger patients.[5] When Lennox-Gastaut develops later in life, seizures have a reduced effect on intellectual development, as the brain is thought to have already progressed beyond certain critical developmental stages.[13]

CLINICAL NEED and BURDEN OF DISEASE

Lennox-Gastaut syndrome is estimated to occur in 0.1-0.28 people per 100,000 and accounts for approximately 1 to 5% of all paediatric epilepsy cases.[6,14] The annual incidence is estimated as 2 per 100,000 in children.[6] In 2016 in the European Union, Lennox-Gastaut syndrome affected approximately 2 in 10,000 people[3] and it is estimated that 23,000 to 31,000 people in Europe have the condition.[7] Lennox-Gastaut syndrome incidence is five times higher in males than females.[15] At the time of diagnosis, cognitive impairments are clinically apparent in 20 to 60% of patients[5] and within five years of onset, significant intellectual problems are evident in 75 to 95% of cases.[9]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Epilepsies: diagnosis and management (CG137). January 2012.
- NICE quality standard. Epilepsy in children and young people (QS27). February 2013.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Paediatric Neurosciences: Neurosurgery. E09/S/a.
- NHS England. 2013/14 NHS Standard Contract for Paediatric Neurosciences: Neurology. E09/S/b.
- NHS England. 2013/14 NHS Standard Contract for Paediatric Neurosciences: Neurodisability E09/S/c.
- NHS England. 2014/14 NHS Standard Contract for Paediatric Neurosciences: Neurorehabilitation. E09/S/d.
- NHS England. 2013/14 NHS Standard Contract for Children's Epilepsy Surgery Service (CESS). E09/S/e

OTHER GUIDANCE

- Ostendorf AP, Ng YT. Treatment-resistant Lennox-Gastaut syndrome: therapeutic trends, challenges and future directions. *Neuropsychiatric Disease and Treatment*. 2017;13:1131.

CURRENT TREATMENT OPTIONS

Lennox-Gastaut syndrome is considered one of the most difficult sub-types of epilepsy to treat as the seizures associated with it are generally refractory to current treatment options available. In order to treat the various types of seizures, treatment often revolves around the combination of multiple types of anti-epileptic drugs, which themselves can be associated with serious side effects in multidrug, high-dose regimens.[6]

The current treatment options are as follows, for adjunctive treatment in children, young people and adults with Lennox-Gastaut syndrome:

- If sodium valproate is ineffective or not tolerated, lamotrigine can be offered.
- If adjunctive treatment is not effective or tolerated then rufinamide and topiramate may be considered by tertiary specialists.
- Carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine and vigabatrin should not be offered for treatment.
- Felbamate (unlicensed) should only be offered in centres where tertiary epilepsy specialist care is provided and when treatment with all other anti-epileptic drugs previously recommended are ineffective or not tolerated.[16]

- Clobazam (unlicensed) is commonly used in tertiary care centres as adjunctive therapy.[a]

Children who suffer from repeated drop attacks can undergo epileptic surgery (corpus callostomy or vagus nerve stimulation) as an option to reduce the number and severity of seizures, although this will not make them seizure free.[14]

EFFICACY and SAFETY

Trial	GWPCARE3, GDCT0222770, NCT02224560, GWEP1414; patient group; higher dose cannabidiol vs lower dose cannabidiol vs placebo; phase III	GWPCARE4, GDCT0222781, NCT02224690, GWEP1423 patient group; cannabidiol vs placebo; phase III	GDCT0222800, NCT02224573, GWEP1415, phase III patient group; cannabidiol only; phase III extension (both trials)
Sponsor	GW Pharmaceuticals Plc	GW Pharmaceuticals Plc	GW Pharmaceuticals Plc
Status	Completed but unpublished	Completed but unpublished	Ongoing
Source of Information	Trial registry[1]	Trial registry[1]	Trial registry[1]
Location	UK, France, Spain and USA	Netherlands, Poland, USA	EU incl. UK, Israel and USA
Design	Randomised, placebo-controlled, double-blind study	Randomised, placebo-controlled, double-blind study	Non-randomised, uncontrolled, single group assignment study
Participants	n=225, aged 2 to 55 years, seizures associated with Lennox-Gastaut syndrome; failed prior therapy, previously treated, refractory (or resistant) disease, uncontrolled disease.	n=171, aged 2 to 55 years, seizures associated with Lennon-Gastaut syndrome; failed prior therapy, previously treated, refractory (or resistant) disease, uncontrolled disease.	n=540 (planned), aged ≥2 years, inadequately controlled Dravet or Lennox-Gastaut syndromes (having participated in one of the cannabidiol core studies).
Schedule	The treatment period consisted of two-week titration period followed by a 12-week maintenance period. Subjects were randomized in 1:1:1 ratio into three arms:	The treatment period consisted of two-week titration period followed by a 12-week maintenance period. Subjects were randomized in 1:1 ratio into two arms: Arm I - Subjects received oral solution (100 mg/ml	Subjects receive cannabidiol solution at a dose of 100 mg/ml orally. The end of treatment takes place once market authorization is granted, a compassionate program becomes available in the country of a particular subject or after a maximum of 3 years' treatment.

[a] Company contact

	Arm I - Subjects received cannabidiol at high dose level (20 mg/kg/day) oral solution (100 mg/mL cannabidiol Arm II - Subjects received cannabidiol at low dose level (10 mg/kg/day) oral solution (100 mg/mL cannabidiol Arm III – Subjects received placebo.	cannabidiol at a dose of 20 mg/kg/day added to current antiepileptic drug treatment. Arm II - Subjects receive placebo oral solution containing the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavouring added to current AED treatment.	
Follow-up	Active treatment for 14 weeks. All subjects offered open label study extension.	Active treatment for 14 weeks. All subjects offered open label study extension.	Treatment until market authorisation, availability of compassionate use programme, or a maximum of 3 years.
Primary Outcomes	Median percentage change from baseline of number of drop seizures during the treatment period up to 14 weeks	Median percentage change from baseline of number of drop seizures during the treatment period up to 14 weeks.	The incidence of adverse events and other assessments as measure of subject safety.
Secondary Outcomes	Number of subjects considered treatment responders defined as those with a ≥25%, ≥50%, ≥75% or 100% reduction in drop seizures from baseline, number of subjects experiencing a > 25% worsening, −25 to +25% no change, 25-50% improvement, 50-75% improvement or >75% improvement in drop seizures from baseline – 0 to 14 weeks, adverse events (AEs), suicidal ideation, abuse liability, cannabis withdrawal effects. Note: this is not an exhaustive list [7/30]	Number of subjects considered treatment responders defined as those with a ≥25%, ≥50%, ≥75% or 100% reduction in drop seizures from baseline, number of subjects experiencing a > 25% worsening, −25 to +25% no change, 25-50% improvement, 50-75% improvement or > 75% improvement in drop seizures from baseline – 0 – 14 weeks, percentage change from baseline in number of non- drop seizures (average per week) 0-14 weeks, percent change from baseline in quality life. Note: this is not an exhaustive list [5/28]	Mean change in quality of life, relative to the pre-randomization baseline of the core study, if assessed during the core study. Changes in the Caregiver Global Impression of Change (CGIC) or Subject Global Impression of Change score, relative to the pre-randomization baseline of the core study, if assessed during the core study, mean percentage change in the frequencies of sub-types of seizures, relative to the pre-randomization baseline of the core study. Mean percentage change in total convulsive seizure frequency, relative to the pre-randomization baseline of the core study. Note: this is not an exhaustive list [4/24]

Key Results	Subjects in both cannabidiol arms achieved a statistically significant reduction in median monthly drop seizure frequency vs placebo (20mg/kg: 42% Vs. 17% [P=0.0047] and 10mg/kg: 37% Vs. 17% [P=0.0016])	Subjects in the cannabidiol arm achieved a statistically significant reduction in median monthly drop seizure frequency vs placebo (20mg/kg: 44% Vs. 22% [P=0.0135]).	-
Adverse effects (AEs)	Most were mild or moderate in nature, and most often reported AEs were sleepiness and decreased appetite.	The most common adverse events (reported in >10% of cannabidiol-treated subjects) included diarrhoea, somnolence, decreased appetite, pyrexia, and vomiting.	-
Expected reporting date	-	-	On going

ESTIMATED COST and IMPACT

COST

The cost of cannabidiol is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: *improved quality of life for carers and improved patient convenience*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

INFORMATION FROM

Information was received by the company.

GW Pharmaceuticals did not enter information about this technology onto the *UK PharmaScan* database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. *UK PharmaScan* is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use *UK PharmaScan* so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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