

**NIHR Innovation Observatory
Evidence Briefing: December 2017****Cannabidiol (Epidiolex®) for tuberous sclerosis
complex - add-on therapy**

NIHRIO (HSRIC) ID: 11888

NICE ID: 9625

LAY SUMMARY

Tuberous sclerosis or tuberous sclerosis complex (TSC) is a rare genetic condition that causes mainly non-cancerous (benign) tumours to develop in different parts of the body. The tumours caused by tuberous sclerosis can result in a range of associated health problems. These problems can range from mild to severe, and it is possible to have only a few of these problems or a wide range of problems. TSC often affects the brain causing epilepsy – a condition that causes seizures (fits). Seizures are the most common presenting sign of TSC. The majority of TSC patients experience seizure onset within the first year of life. Adults without seizure history continue to be at risk and some adults in this subgroup will develop epilepsy later in life.

Cannabidiol is a medicine that is being developed for the treatment of TSC patients who experience inadequately-controlled seizures. It is being developed as an oral medicine to be added to existing treatment options for TSC ('add-on therapy'). Cannabidiol has a unique chemical structure that makes it prevent or stop seizures and is thought to have cumulative effect. If licensed, cannabidiol will offer an add-on treatment option for patients with TSC who experience inadequately-controlled seizures.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Tuberous sclerosis complex (patients who experience inadequately-controlled seizures) - add-on therapy

TECHNOLOGY

DESCRIPTION

Cannabidiol (Epidiolex; GWP42003-P) is a cannabinoid product and a proprietary oral solution of pure plant-derived cannabidiol (CBD).¹ Cannabinoids act on multiple systems and is understood to interact with many neurotransmitter and neuromodulator systems. Cannabinoids act as ligands (a small molecule able to dock onto the binding site of a protein) conferring their ability to modulate a receptor's behaviour and consequently their downstream biological pathways. CBD is a structurally novel anti-convulsant although the exact mechanism of action by which it produces its anticonvulsant effects is unknown. CBD may exert a cumulative anti-convulsant effect, modulating a number of endogenous systems including, but not limited to, neuronal inhibition (synaptic and extrasynaptic GABA channels), modulation of intracellular calcium (TRPV, VDAC, GPR55), and possible anti-inflammatory effects (adenosine). Those mechanisms are under investigation by the manufacturer. There are additional mechanisms which are also under exploration. These include glycine modulation and serotonin agonism.²

In the phase III clinical trial (NCT02544763), cannabidiol (100 mg/ml oral solution twice daily) is administered in two doses: 25 mg/kg/day or 50 mg/kg/day over a treatment period of 16 weeks.³

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

Cannabidiol is at phase III stage of development for the treatment of Dravet syndrome, Lennox-Gastaut syndrome, and infantile spasms.⁴

INNOVATION and/or ADVANTAGES

There are currently limited or, in some cases, no approved treatment options to treat rare, treatment-resistant epilepsy conditions. Cannabidiol is a structurally novel anti-convulsant under investigation. If licensed cannabidiol will offer a new add-on treatment option for patients with tuberous sclerosis complex (TSC) who experience inadequately-controlled seizures.^{1,2}

DEVELOPER

GW Research Ltd.

AVAILABILITY, LAUNCH or MARKETING

Cannabidiol is a designated orphan drug in the USA for tuberous sclerosis complex in April 2016.⁵

PATIENT GROUP

BACKGROUND

Tuberous sclerosis or tuberous sclerosis complex (TSC), is a rare genetic condition that causes mainly non-cancerous (benign) tumours to develop in different parts of the body. These tumours can occur in the skin, brain, kidneys, lungs and other organs, in some cases leading to significant health problems.^{6,7}

Mutations in the TSC1 or TSC2 gene can cause tuberous sclerosis complex. People with tuberous sclerosis complex are born with one mutated copy of the TSC1 or TSC2 gene in each cell. A second TSC1 or TSC2 mutation typically occurs in multiple cells over an affected person's lifetime. These genes are involved in regulating cell growth, and the mutations lead to uncontrolled growth and multiple tumours throughout the body.^{6,7}

The tumours caused by tuberous sclerosis can result in a range of associated health problems. These problems can range from mild to severe, and it is possible to have only a few of these problems or a wide range of problems. TSC often affects the brain causing epilepsy – a condition that causes seizures (fits). Seizures are the most common presenting sign of TSC, occurring in about 90% of patients. Also, TSC in the brain causes learning disabilities or behavioural problems such as hyperactivity or an autistic spectrum disorder. Benign brain tumours can also develop in people with tuberous sclerosis complex; these tumours can cause serious or life-threatening complications.^{6,7,8} The majority (63%) of TSC patients experience seizure onset within the first year of life. Adults without seizure history continue to be at risk, with 12% of adults in this subgroup later developing epilepsy. Epilepsy develops in 96%–99% of TSC patients with a single seizure. Infantile spasm is the most common initial seizure subtype, although 54% of TSC patients develop multiple seizure types, including simple partial, complex partial, and secondary generalized seizures.⁹

Patients with TSC may also have other symptoms such as skin abnormalities which occur in most affected people. These include patches of light-coloured or thickened skin, or red acne-like spots on the face. Kidney tumours are common in people with TSC; these growths can cause severe problems with kidney function and may be life-threatening in some cases. Additionally, tumours can develop in the heart, lungs, and the light-sensitive tissue at the back of the eye (the retina).^{6,7}

There is a 50% chance of passing TSC from parents to their biological children. However, the severity of the condition may vary i.e. a parent with tuberous sclerosis may have a child who has a milder or more severe form of the disorder.¹⁰

Depending on the location and size of the tumours, TSC can cause severe or life-threatening complications. These complications include:¹⁰

- Hydrocephalus: build-up of fluid in the cavities (ventricles) deep within the brain occurs due to the blockage of the flow of cerebral spinal fluid within the brain. This condition is called hydrocephalus. Various signs and symptoms include an unexpectedly large head size, nausea, headaches and behaviour changes.
- Heart complications: growths in the heart, usually in infants, can block blood flow or cause problems with heart rhythm (dysrhythmia).
- Kidney damage: growths in the kidney can be large and cause potentially serious — even life-threatening — kidney problems. Growths in the kidney can cause high blood pressure or bleeding or lead to kidney failure. Rarely, kidney growths can become cancerous.
- Lung failure: growths in the lungs can lead to a collapsed lung or fluid around the lungs that interferes with lung function.

- Increased risk of cancerous (malignant) tumours in the kidneys and brain.
- Vision damage: growths in the eye can interfere with vision if they block too much of the retina, though this is rare.

CLINICAL NEED and BURDEN OF DISEASE

TSC is the second most common neuro-cutaneous disease after neurofibromatosis type-1.¹¹ Estimates indicate that 2,000,000 people have TSC worldwide.¹² In the UK, 10 babies are born with TSC each month¹³ and it is estimated that in 2012 there were 8,000 people with TSC.¹⁴ A meta-analysis of 380 TSC patients from four distinct populations (American, British, Polish, and Taiwanese) showed that the frequency of TSC1 mutations was twice as high in the American and British populations (26.5% and 22.4% respectively).¹⁵ The prevalence of lifetime epilepsy in people with TSC is high (80%–90% of affected individuals).¹⁶

A retrospective cohort study (Kingswood 2016)¹⁷ was conducted in the UK on TSC patients in the Clinical Practice Research Datalink (CPRD) and linked Hospital Episodes Statistics (CPRD-HES) who were identified between 1987 and 2013. The number of TSC patients identified was 334. The mean age was 30.3 years. Epilepsy was reported frequently in 77% of paediatric and adult 66% patients.¹⁷ NHS Digital hospital episode statistics for England 2016/17 shows that there were 321 hospital admissions for tuberous sclerosis (ICD 10 code: Q85.1), 362 Finished Consultant Episodes (FCE), and 498 FCE bed days.¹⁸

Analysis done by Kingswood (2016) of the Office of National Statistics (ONS) mortality register showed that only 5% of the TSC cohort (n = 16) had died. These patients had a mean age at death of 57.5 years.¹⁷ Another retrospective study was conducted in the UK on patients with TSC who attended Bath TSC clinic between 1981 and 2015. Identified patients were 284. Sixteen patients died from complications of TSC of which four from sudden unexpected death in epilepsy. This suggested that sudden unexpected death in epilepsy is an important cause of mortality in patients with TSC.¹⁹

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline. Epilepsies: diagnosis and management (CG137). January 2012 (updated: February 2016).

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Clinical Commissioning Policy: Everolimus for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex. 16066/P. December 2016.

OTHER GUIDANCE

- International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference.²⁰
- International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference.²¹

CURRENT TREATMENT OPTIONS

TSC is a lifelong condition that requires long-term care and support from a range of different healthcare professionals. If a child is affected, an individual care plan will be drawn up to address any needs or problems they have. Medications to control the seizures (anti-epileptic drugs) will usually be tried first, although they are not always effective for people with tuberous sclerosis. Two medicines might be prescribed to be taken at once. If the medication does not control seizures then the patient may need to have surgery to remove the brain tumour that may be causing the seizures, vagus nerve stimulations, ketogenic diet or a modified version of ketogenic diet.⁶

Recommendations by the International Tuberous Sclerosis Complex Consensus Group on brain tumours management in patients with TSC include:²¹

- Obtain magnetic resonance imaging (MRI) of the brain every 1-3 years in asymptomatic TSC patients younger than age 25 years to monitor for new occurrence of subependymal giant cell astrocytoma (SEGA). Patients with large or growing SEGA, or with SEGA causing ventricular enlargement but yet are still asymptomatic, should undergo MRI scans more frequently.
- Surgical resection should be performed for acutely symptomatic SEGA. Cerebral spinal fluid diversion (shunt) may also be necessary. Either surgical resection or medical treatment with mammalian target of rapamycin complex (mTOR) inhibitors may be used for growing but otherwise asymptomatic SEGA.
- Obtain routine electroencephalograph (EEG) in individuals with known or suspected seizure activity. The frequency of routine EEG should be determined by clinical need rather than a specific defined interval. Prolonged video EEG, 24 hour or longer, is appropriate when seizure occurrence is unclear or when unexplained sleep, behavioural changes, or other alteration in cognitive or neurological function is present.
- Vigabatrin is the recommended first-line therapy for infantile spasms. Adrenocorticotropin hormone (ACTH) can be used if treatment with vigabatrin is unsuccessful. Anticonvulsant therapy of other seizure types in TSC should generally follow that of other epilepsies. Epilepsy surgery should be considered for medically refractory TSC patients, but special consideration should be given to children at younger ages experiencing neurological regression and is best if performed at epilepsy centres with experience and expertise in TSC.

EFFICACY and SAFETY

Trial	GWPCARE6, NCT02544763; aged 1- 65 years; cannabidiol 25 mg/kg/day vs cannabidiol 50 mg/kg/day vs placebo; phase III	GWPCARE6, NCT02544750; aged 1- 65 years; cannabidiol; phase III extension
Sponsor	GW Research Ltd	GW Research Ltd
Status	Ongoing, recruiting.	Ongoing, recruiting by invitation.
Source of Information	Trial registry,3 global data. ²²	Trial registry. ²³
Location	USA	USA
Design	Double-blind, randomized, placebo-controlled.	Open label, single group assignment.
Participants	n=210 (planned); aged 1-65 years; male and females; well-documented clinical history of epilepsy; clinical diagnosis of TSC according to the criteria agreed by the 2012 International TSC Consensus Conference; all medications or interventions for epilepsy (including ketogenic diet and any neurostimulation devices for epilepsy) must have been stable for 1 month prior to screening.	n=210 (planned); aged 1-65 years; male and females; completion of the GWEP1521 blinded phase.
Schedule	Randomised to 25 mg/kg/day cannabidiol (100 mg/mL cannabidiol oral solution taken twice daily (morning and evening)); or 50 mg/kg/day cannabidiol (100 mg/mL cannabidiol oral solution taken twice daily (morning and evening)); or placebo.	Participants will receive 100 mg/ml cannabidiol oral solution taken twice daily (morning and evening). Participants will be dosed up to a maximum of 50 mg/kg/day. Dose may be lower if Investigator judges benefit and/or tolerability issues.
Follow-up	Active treatment for 16 weeks, follow-up for 2 years.	Follow-up for 2 years.
Primary Outcomes	Change in seizure frequency [Time Frame: Baseline and average over the 16-week treatment period (or up to the point of withdrawal)]	Incidence of adverse events [Time Frame: From OLE screening until market authorization is granted for cannabidiol in TSC (anticipated to be 2 years after the OLE trial start date)]
Secondary Outcomes	Time Frame: 16 weeks <ul style="list-style-type: none"> • Number of treatment responders • Number of participants with worsening, no change, or improvements in seizure frequency • Change in composite focal seizure score 	Time Frame: Baseline and once market authorization is granted for GWP42003-P in TSC (anticipated to be 2 years after the OLE trial start date): <ul style="list-style-type: none"> • Change in seizure frequency • Change in composite focal seizure score

	<ul style="list-style-type: none"> • Change in number of seizure-free days • Change in number of seizures by subtype • Change in number of infantile/epileptic spasms • Change in use of rescue medication • Change in number of episodes of status epilepticus • Change in duration of seizures by subtype • Change in overall condition as assessed by the participant/caregiver • Change in overall condition as assessed by the physician • Change in Vineland-II score • Change in Wechsler score by subtest • Change in Behaviour Checklist score • Change in Social Communication Questionnaire score • Change in Quality of Life score • Change in serum IGF-1 levels • Number of participants with changes in Tanner stage <p>Time Frame: Screening to End of Trial (up to Week 21)</p> <ul style="list-style-type: none"> • Incidence of adverse events <p>Time Frame: Screening to End of Dosing (up to Week 17)</p> <ul style="list-style-type: none"> • Incidence of suicidality 	<ul style="list-style-type: none"> • Change in number of seizure-free days • Change in number of seizures by subtype • Change in number of infantile/epileptic spasms • Change in use of rescue medication • Change in number of episodes of status epilepticus • Change in Vineland-II score • Change in Wechsler score by subtest • Change in Behaviour Checklist score • Change in Social Communication Questionnaire score • Change in Quality of Life score • Change in serum IGF-1 levels <p>Time Frame: Once market authorization is granted for cannabidiol in TSC (anticipated to be 2 years after the OLE trial start date):</p> <ul style="list-style-type: none"> • Number of treatment responders • Number of participants with worsening, no change, or improvements in seizure frequency • Change in duration of seizures by subtype • Change in overall condition as assessed by the participant/caregiver • Change in overall condition as assessed by the physician • Number of participants with changes in Tanner stage <p>Time Frame: From OLE screening until market authorization is granted for cannabidiol in TSC (anticipated to be 2 years after the OLE trial start date):</p> <ul style="list-style-type: none"> • Incidence of suicidality
Key Results	-	-
Adverse effects (AEs)	-	-
Expected reporting date	Study completion date reported as September 2018.	Study completion date reported as September 2020.

ESTIMATED COST and IMPACT

COST

The cost of cannabidiol is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|---|--|
| <input type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other: | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|--|
| <input type="checkbox"/> Increased use of existing services | <input checked="" type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other | <input type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|--|---|
| <input checked="" type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs | <input type="checkbox"/> Other reduction in costs |
| <input type="checkbox"/> Other | <input type="checkbox"/> None identified |

OTHER ISSUES

- | | |
|---|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified | <input checked="" type="checkbox"/> None identified |
|---|---|

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