A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P; CBD) as adjunctive treatment for seizures associated with Lennox- Gastaut syndrome in children and adults

Published: 31-03-2015
Last updated: 14-04-2024

Primary objective: To evaluate the efficacy of GWP42003-P as adjunctive treatment inreducing the number of drop seizures when compared with placebo, inpatients with LGS.Drop seizure is defined as an attack or spell (atonic, tonic or tonic-clonic)…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Seizures (incl subtypes)
Study type	Interventional

Summary

ID

NL-OMON42107

Source
ToetsingOnline

Brief title
GWEP1423

Condition

- Seizures (incl subtypes)

Synonym
epilepsy, Lennox Gastaut Syndrome

Research involving
Human

Sponsors and support

Primary sponsor: GW Research Ltd.
Source(s) of monetary or material Support: GW Pharmaceuticals

Intervention

Keyword: cannabidiol, epilepsy, Lennox Gastaut syndrome

Outcome measures

Primary outcome

The primary endpoint is the mean percentage change from baseline in number of drop seizures (average per week) during the maintenance period (Day 15 to the end of the evaluable period) in patients taking GWP42003-P compared with placebo.

Secondary outcome

The following endpoints will be compared between treatment groups over the 12-week, double-blind maintenance period:

* Percentage change from baseline in number of drop seizures (average per week) during the Weeks 1*4, 5*8 and 9*12.

* Number of patients considered treatment responders, defined as those with a *25%, *50%, *75%, or 100% reduction in drop seizures from baseline. Summaries will be presented overall and four-weekly.

* Number of patients experiencing a >25% worsening, *25 to +25% no change, 25* 50% improvement, 50*75% improvement or >75% improvement in drop seizures from baseline.

* Percentage change from baseline in number of non-drop seizures (average per

week).

* Percentage change from baseline in the frequencies of subtypes of seizures (average per week).

* Changes from baseline in duration of seizure subtypes as assessed by the Subject/Caregiver Global Impression of Change in Seizure Duration (S/CGICSD).

* Changes from baseline in number of episodes of status epilepticus.

* Changes from baseline in number of inpatient hospitalizations due to epilepsy.

* Changes from baseline in quality of life as assessed by the Quality of Life in Childhood Epilepsy (QOLCE), for patients aged between two and 18 years of age, or Quality of Life in Epilepsy, version 2, (QOLIE-31-P) for patients aged 19 years and older.

* Changes from baseline in the Subject/Caregiver Global Impression of Change (S/CGIC) score.

* Change from baseline in adaptive behavior as measured with the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II).

* Change from baseline in cognitive function as measured with the Cognitive Assessment Battery.

* Changes from baseline in Sleep Disruption 0*10 Numerical Rating Scale (0*10 NRS) score.

* Changes from baseline in Epworth Daytime Sleepiness Scale (EDSS) score.

* Change from baseline in growth and development by measurement of height, weight, , insulin-like growth factor-1 (IGF-1) levels, menstruation and Tanner Staging.

Pharmacokinetic:

* GWP42003-P: The plasma concentration/time curve of CBD and its major metabolites will be described following single and multiple doses of GWP42003-P, with the aim being to define:

* Cmax

* tmax

* AUC0-*, AUC0-t

* t*

The safety profile of GWP42003-P compared with placebo will also be assessed by measuring:

* AEs.

* Clinical laboratory parameters.

* Columbia-Suicide Severity Rating Scale (C-SSRS) score.

* Vital signs.

* Physical examination parameters.

* 12-lead electrocardiogram (ECG).

* Cannabis Withdrawal Scale (CWS) or Pediatric Cannabinoid Withdrawal Scale (PCWS) score, as appropriate.

* Abuse liability.

Study description

Background summary

Given the limitations of current synthetic AEDs, it has been hypothesized that CBD

can be tested for efficacy in children with pharmacoresistant epilepsy. A recent parent survey has reported that 84% of children with treatment-resistant epilepsy
experienced a reduction in seizures while taking CBD-enriched cannabis, with over
half of those reporting >80% reduction in seizure frequency. The majority of children had been diagnosed with DS, two thirds of which experienced *50% reduction in seizure frequency with one (8.3%) achieving complete seizure freedom.
However, one child diagnosed with LGS achieved a >80% reduction in seizure frequency. The CBD-enriched cannabis was behaviorally well tolerated and children
often experienced improved sleep, increased alertness and better mood.

Study objective

Primary objective: To evaluate the efficacy of GWP42003-P as adjunctive treatment in
reducing the number of drop seizures when compared with placebo, in patients with LGS.
Drop seizure is defined as an attack or spell (atonic, tonic or tonic-clonic) involving the entire body, trunk or head that led or could
have led to a fall, injury, slumping in a chair or hitting the patient*s head on a surface.

secondary objective: To assess the following in LGS patients taking GWP42003-P as
adjunctive treatment, when compared with placebo:
Key:
* Number of patients drop seizure-free.
* Responder rate, in terms of reduction in drop seizures.
* Reduction in the number of non-drop seizures.
* Frequency of subtypes of seizures.
* Safety and tolerability of GWP42003-P through monitoring of:
* Adverse events (AEs).
* Suicidal ideation.
* Abuse liability.
* Cannabis withdrawal effects.
* Clinical laboratory tests.
* Vital signs.
Other:
* Number of episodes of status epilepticus.
* Need for hospitalization due to epilepsy.
* Change in duration of subtypes of seizures.
* Sleep disruption and daytime sleepiness.
* Quality of life.
* Adaptive behavior.

* Cognitive function.
* Growth and development
* To determine the pharmacokinetics of GWP42003-P and its major metabolites following single and multiple doses of GWP42003-P.

Study design

This study is a 1:1 randomized, double-blind, 14-week comparison of GWP42003-P versus placebo. The treatment period will consist of a two-week titration period followed by a 12-week maintenance period. The treatment period will be followed by a 10-day taper period and a four-week follow-up period. The study will aim to determine the efficacy, safety and tolerability of GWP42003-P compared with placebo. The dose will be as recommended by the Data Safety Monitoring Committee (DSMC) after assessment of safety and pharmacokinetic data from Part A of study GWEP1332. The first patient will not enroll into this study until the DSMC has reviewed the safety data from Part A of study GWEP1332.
Following study completion, all patients will be invited to continue to receive GWP42003-P in an open label extension (OLE) study (under a separate protocol).

Intervention

A total of 80 patients will be enrolled to receive GWP42003-P (the active investigational medicinal product [IMP]) or placebo on a 1:1 basis (40 patients per treatment group).

Study burden and risks

The side effects listed below relate to the 107 patients who previously took either CBD BDS or pure CBD study medications. The study medication is a different formulation of pure CBD. The side effects marked with *** (common) and **** (very common) have been seen in 20 patients who have previously taken study medication of pure CBD, all being classed as common, with the exceptions of headache, feeling irritable and diarrhea which were very common.

Very common side effects which may affect more than one person in every 10 are: Headache**, feeling sick*, diarrhea**.

Common side effects which may affect more than one person in every 100 are: Mouth problems (including, pain, discomfort, dry mouth, loss of taste or change in taste*, reduction in or loss of sensation), feeling tired*, feeling drunk or abnormal, cold symptoms*, feeling irritable**, feeling depressed or confused, eating less than usual*, feeling dizzy, body pain* (including back pain* and neck pain*), abnormal dreams*, nose bleed, sickness*, bloated* or tummy pain*,

constipation, indigestion*, feeling weak or unwell, flushing, worsening of multiple sclerosis, muscle spasms.

Uncommon side effects which may affect more than one person in every 1000 are: Ear pain*, vertigo*, belching*, loss of bowel control, difficulty with the pill size, tooth infection*, sore throat*, fall*, joint pain*, tearfulness, urgency to pass motions*, increased frequency in passing water*, abnormal moods*, trouble sleeping*, rashes*, itching*, change in liver function blood test values* or hematology blood test values*.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

* Patient and/or parent(s)/legal representative must be willing and able to give informed assent/consent for participation in the study.;* Patient and their caregiver must be willing and able (in the investigator*s opinion) to comply with all study requirements.;* Patient must be male or female aged between two and 55 years (inclusive).;* Patient must have a clinical diagnosis of of LGS. This includes written documentation of having met electroencephalogram (EEG) diagnostic criteria during the patient*s history and evidence of more than one type of generalized seizure, including drop seizures (atonic, tonic or tonic-clonic), for at least six months. Care should be taken not to include benign myoclonic epilepsy of infancy, atypical benign partial epilepsy (pseudo-Lennox syndrome), or continuous spike-waves of slow sleep (CSWS);* Patients who have a history of slow (<3.0 Hz) spike-and-wave pattern in an EEG prior to the enrollment into the baseline period.;* Patients must have at least two drop seizures each week during the 28-day baseline period.;* Patients should be refractory; that is having documented failures on more than one antiepileptic drug (AED).;* Patient must be taking one or more AEDs at a dose which has been stable for at least four weeks prior to screening.;* All medications or interventions for epilepsy (including ketogenic diet and vagus nerve stimulation [VNS]) must have been stable for four weeks prior to screening and patient is willing to maintain a stable regimen throughout the study. The ketogenic diet and VNS treatments are not counted as an AED.;* Patient and/or parent(s)/legal representative is willing to allow his or her primary care practitioner and consultant to be notified of participation in the study.

Exclusion criteria

* Etiology of patient's seizures is a progressive neurologic disease. Patients with tuberous sclerosis will not be excluded from study participation, unless there is a progressive tumor.;* Patient has had an anoxic episode requiring resuscitation within six months of screening.;* Patient has clinically significant unstable medical conditions other than epilepsy.;* Patient has had clinically relevant symptoms or a clinically significant illness in the four weeks prior to screening or randomization, other than epilepsy.;* Patient has clinically significant abnormal laboratory values, in the investigator*s opinion, at screening or randomization.;* Patient has clinically relevant abnormalities in the ECG measured at screening or randomization.;* Patient has any concurrent cardiovascular conditions, which will, in the investigators opinion, interfere with the ability to assess their ECGs.;* Patient has a history or presence of alcohol or substance abuse within the last two years prior to the study or daily consumption of five or more alcohol-containing beverages.;* Patient is currently using or has in the past used recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex®) within the three months prior to study entry. ;* Patient is unwilling to abstain from using recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex) during the study.;* Patient has a history of symptoms (e.g., dizziness, light-headedness, blurred vision, palpitations, weakness, syncope) related to a drop in blood pressure due to postural changes.;* Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, such as sesame oil.;* Female patient is of

child bearing potential and must have a negative pregnancy test and be willing and able to use a reliable method of contraception throughout the trial and for three months after last dose. Male patient*s partner is of child bearing potential; unless willing to ensure that they or their partner use a highly effective method of contraception. In the context of this trial, a highly effective method is defined as those which result in low failure rate (i.e., less than 1% per year) when used consistently and correctly such as: combined or progesterone only oral contraceptives, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner or sexual abstinence;* Female patient who is pregnant, lactating or planning pregnancy during the course of the study and for three months thereafter.;* Patient has been part of a clinical trial involving another IMP in the previous six months.;* Any other significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, may influence the result of the study, or affect the patient*s ability to participate in the study.

* Patient has significantly impaired hepatic function at screening (Visit 1) or randomization (Visit 2) (Alanine aminotransferase [ALT] >5 x upper limit of normal [ULN] and total bilirubin [TBL] >2 x ULN) OR the ALT or Aspartate aminotransferase (AST) >3 x ULN and (TBL >2 x ULN or international normalized ratio [INR] >1.5). This criterion can only be confirmed once the laboratory results are available; patients randomized into the study who are later found to meet this criterion must be withdrawn from the study.;* Following a physical examination, the patient has any abnormalities that, in the opinion of the investigator, would prevent the patient from safe participation in the study.;* Any history of suicidal behavior or any suicidal ideation of type four or five on the C-SSRS in the last month or at screening.;* Patient is unwilling to abstain from donation of blood during the study.;* There are plans for the patient to travel outside their country of residence during the study.;* Patient has previously been randomized into this study.;* Patient is taking more than four concurrent AEDs.;* Patient has taken corticotropins in the six months prior to screening.;* Patient is currently taking long-term systemic steroids (excluding inhaled medication for asthma treatment) or any other daily medication known to exacerbate epilepsy. An exception will be made for prophylactic medication, for example, idiopathic nephrotic syndrome or asthma. ;* Patient is taking felbamate, and they have been taking it for less than one year prior to screening.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-10-2015
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Epidiolex
Generic name:	cannabidiol

Ethics review

Approved WMO Date:	31-03-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-09-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-10-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-002941-23-NL
ClinicalTrials.gov	NCT02224690
CCMO	NL51799.041.15