A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome.

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To assess the efficacy of GWP42003-P as an adjunctive antiepileptic treatment compared with placebo, with respect to the percentage change from baseline during the treatment period of the study in convulsive seizure frequency. The dose response...

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

Summary

ID

NL-OMON44663

Source
ToetsingOnline

Brief title
GWEP1424

Condition

- Seizures (incl subtypes)

Synonym
Dravet syndrome

Research involving
Human

Sponsors and support

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

Intervention

Keyword: cannabidiol, Dravet syndrome, epilepsy

Outcome measures

Primary outcome

The primary endpoint is the mean percentage change from baseline in total convulsive seizure frequency during the treatment period (Day 1 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 14-week, double-blind treatment period:

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

- Number of patients considered treatment responders, defined as those with a >=25%, >=50% or >=75% reduction in convulsive seizures from baseline (overall and four-weekly).

- Number of patients who are convulsive seizure free.

- Percentage changes from baseline in total non-convulsive seizure frequency.

- Change in types of seizures.

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

- Changes from baseline in duration of seizure subtypes as assessed by the

Caregiver Global Impression of Change in Seizure Duration

(CGICSD).

- Changes from baseline in usage of rescue medication.

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

- 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.

- Changes from baseline in the Quality of Life in Childhood Epilepsy (QOLCE) score.

- Changes from baseline in the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II) score.

- Change from baseline in cognitive function as measured with a cognitive assessment battery.

- Change from baseline in growth and development by measurement of height, weight, insulin-like growth factor-1 (IGF-1) levels and Tanner Staging (for patients aged 10-17 [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty).

- Changes from baseline in the Caregiver Global Impression of Change (CGIC) score.

PK:

- 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:

- Peak plasma concentration (Cmax).

- Time to peak concentration (tmax).

- Area under the plasma concentration curve from time zero to infinity (AUC(0-*)) or to the last measurable concentration (AUC(0-tz)).

- Terminal half-life (t*).

- Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available.

The safety profile of GWP42003-P compared with placebo will also be the assessed at each Dose Level by measuring:

- Adverse events (AEs).

- Vital signs.

- Physical examination parameters.

- 12-lead Electrocardiogram (ECG).

- Clinical laboratory parameters.

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

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

- Abuse liability.

- Effects on menstruation cycles (in females).

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 Dravet Syndrome, two thirds of which experienced >=50% reduction in seizure frequency with one patient (8.3%) achieving complete seizure freedom. The CBD-enriched cannabis was behaviorally well tolerated and children often experienced improved sleep, increased alertness, and better mood.

Study objective

To assess the efficacy of GWP42003-P as an adjunctive antiepileptic treatment compared with placebo, with respect to the percentage change from baseline during the treatment period of the study in convulsive seizure frequency. The dose response effect between two GWP42003-P Dose Levels (10 mg/kg/day and 20 mg/kg/day) and placebo will also be explored. Convulsive seizures are defined as tonicclonic, tonic, clonic or atonic and non-convulsive seizures as myoclonic, partial or absence.

• To assess changes from baseline in non-convulsive seizure frequency, duration, usage of rescue medication, number of inpatient hospitalizations due to epilepsy, sleep disruption, daytime sleepiness, quality of life, growth and development, and conduct behavioral and cognitive assessments in patients taking GWP42003-P as an adjunctive treatment, when compared with placebo.
• To determine the pharmacokinetics (PKs) of cannabidiol (CBD) and its major metabolites following single and multiple doses of GWP42003-P.
• To determine effects of GWP42003-P on plasma concentrations of concomitant antiepileptic drugs (AEDs), where available.
• To assess the safety of both GWP42003-P doses when compared with placebo.

Study design

This study is a 1:1:1 randomized, double-blind, 14-week comparison of two Dose Levels of GWP42003-P (10 mg/kg/day and 20 mg/kg/day) 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 fourweek follow-up period. The study will aim to determine the efficacy, safety and tolerability of two Dose Levels of GWP42003-P compared with placebo. Patients in the placebo group will be split into two equivalent cohorts: half receiving 10 mg/kg/day dosing volumes and half receiving 20 mg/kg/day dosing volumes. 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 150 patients will be randomized to receive one of two Dose Levels (10 mg/kg/day or 20 mg/kg/day) of active investigational medicinal product (IMP) or placebo on a 1:1:1 basis (50 patients per treatment group). The randomization will be stratified by age group (2-5 years, 6-12 years and 13-18 years). Patients in the placebo group will be split into two cohorts (25 receiving 10 mg/kg/day dosing volumes and 25 receiving 20 mg/kg/day dosing volumes), but it is assumed that these two cohorts can be pooled for the analyses of efficacy.

Study burden and risks

Like all medicines, the active medication may cause side effects in some people. The following side effects have been seen in the 107 adult patients who have previously taken either CBD BDS or pure CBD study medication. It should be noted that 87 of these patients took a formulation containing small amounts of other cannabinoids including THC and so may have resulted in a higher incidence of side effects than with the study medication your child is using. They have been categorized by the likelihood of them occurring, and listed in the order they have most commonly been reported. A lot of these effects have also been seen with the placebo medication. The side effects with a * have been seen in 20 patients who have previously taken the same study medication as the one used in this study, pure CBD, with all side effects 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 (excluding the very common side effects above): Mouth problems (including, pain, discomfort, dry mouth, loss of sense of taste or change in sense of 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 (excluding the common and very common side effects above): Ear pain*, vertigo*, belching*, loss of bowel control, difficulty with the capsule 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 tests* or

hematology blood tests*. It may also affect some blood tests*.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

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 18 years
(inclusive).;• Patient must have a documented history of DS which is not completely controlled by current AEDs.;• Patient must be experiencing four or more convulsive seizures (i.e.,

tonic-clonic, tonic, clonic, atonic seizures) during the first 28 days of the baseline period.;• Patient must be taking one or more AEDs at a dose which has/have been stable for at least four weeks.;• 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 and caregiver are 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.;• Patient has completed their Interactive Voice Response System (IVRS) telephone diary on at least 25 days of the baseline period; patients who are non-compliant will be deemed ineligible to continue.

Exclusion criteria

• 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 investigator's 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 ingested alcohol in the 24-hour period prior to the first study visit and/or is unwilling to abstain from drinking alcohol throughout the treatment period.;• Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMPs (e.g., sesame oil).;• Female patient is of child bearing potential or male patient's partner is of child bearing potential; unless willing to ensure that they or their

partner use highly effective contraception for the duration of the study and for three months thereafter. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Such methods include hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner or sexual abstinence.;• Female patient who is pregnant (positive pregnancy test), 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.;• Patient is taking felbamate and they have been taking it for less than one year prior to screening.;• 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), defined as any of the following:
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 x upper limit of normal (ULN).
- ALT or AST >3 x ULN and (total bilirubin [TBL] >2 x ULN or international normalized ratio [INR] >1.5).
- ALT or AST >3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).;• 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.;• 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.;• Any history of suicidal behavior or any suicidal ideation of type four or five on the C-SSRS at 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):	13-04-2015
Enrollment:	30
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	11-11-2014
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	04-03-2015
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-03-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-05-2015

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-08-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-09-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-05-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-07-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-10-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-03-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-05-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-09-2017

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-09-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-12-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-12-2017
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2014-002939-34-NL
ClinicalTrials.gov	NCT02224703
CCMO	NL50788.041.14

Study results

Results posted:	10-09-2019

First publication
11-08-2019