An open label extension study to investigate the safety of cannabidiol (GWP42003-P; CBD) in children and adults with inadequately controlled Dravet or Lennox-Gastaut Syndromes

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To evaluate the long term safety and tolerability of GWP42003-P, as adjunctive treatment, in children and adults with inadequately controlled DS or LGS.All Patients:To evaluate the effect of GWP42003-P, as adjunctive treatment, on:* Quality of life...

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

Summary

ID

NL-OMON45127

Source
ToetsingOnline

Brief title
GWEP1415

Condition

- Seizures (incl subtypes)

Synonym
childepilepsy, dravet syndrome and lennox gastaut syndrome

Research involving
Human

Sponsors and support

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

Intervention

Keyword: cannabinoid, dravet syndrome, lennox gastaut syndrome, open label

Outcome measures

Primary outcome

The safety of GWP42003-P will be assessed by the adverse event (AE) profile and

by evaluating changes in the following, relative to the pre-randomization

baseline of the Core Study:

* Vital signs.

* Physical examination (including height and body weight).

* 12-lead electrocardiogram (ECG).

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

* Cannabis Withdrawal Scale (CWS) or Pediatric Cannabinoid Withdrawal Scale

(PCWS) score, (as appropriate).

* Clinical Laboratory parameters.

The CWS will be administered to patients aged 18 and older while the PCWS will

be administered to patients aged 4*17 (inclusive).

The Children*s C-SSRS will be used for patients aged 6*18 (inclusive) while the

C-SSRS will be used for patients aged 19 and older.

Secondary outcome

All Patients:

* Change in quality of life as measured with Quality of Life in Childhood

Epilepsy (QOLCE) if 18 years of age or younger, or Quality of Life in Epilepsy (QOLIE) if 19 years of age or older, relative to the pre-randomization baseline of the Core Study, if assessed during the Core Study.

* Change in Subject/Caregiver Global Impression of Change (S/CGIC), relative to the pre-randomization baseline of the Core Study.

* Change in adaptive behavior as measured with the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II), relative to the pre-randomization baseline of the Core Study, if assessed during the Core Study.

* Change in the number of inpatient epilepsy-related hospitalizations (number of hospitalizations due to epilepsy in each 28-day period), relative to the pre-randomization baseline of the Core Study.

* Change in the use of rescue medication (number of days used in each 28-day period), relative to the pre-randomization baseline of the Core Study.

* Maintenance of seizure frequency reduction and freedom from seizures during the OLE study.

* Percentage change in the frequency of total seizures, relative to the pre-randomization baseline of the Core Study.

* Number of patients considered treatment responders, defined as those with a * 25%, * 50%, * 75%, or 100% reduction in total seizures, relative to the pre-randomization baseline of the Core Study.

* Number of patients experiencing a > 25% worsening, * 25 to + 25% no change, 25*50% improvement, 50*75% improvement or > 75% improvement in total seizures, relative to the pre-randomization baseline of the Core Study.

* Percentage change in the frequencies of subtypes of seizures, relative to the

pre-randomization baseline of the Core Study.

* Changes in duration of seizure subtypes as assessed by the Subject/Caregiver Global Impression of Change in Seizure Duration (S/CGICSD), relative to the pre-randomization baseline of the Core Study.

* Change in the number of episodes of status epilepticus, relative to the pre-randomization baseline of the Core Study.

* Change in cognitive function as measured with a cognitive assessment battery, relative to the pre-randomization baseline of the Core Study, if assessed during the Core Study.

* Change in growth and development for patients less than 18 years of age 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), relative to the pre-randomization baseline of the Core Study.

* Effects on menstruation cycles (in females).

* Drug abuse liability, as measured by AEs of abuse potential, drug accountability and Study Medication Use and Behavior Survey in patients aged 12 and older.

DS Patients Only:

* Percentage change in total convulsive seizure frequency, relative to the pre-randomization baseline of the Core Study.

* Percentage change in total non-convulsive seizure frequency, relative to the pre-randomization baseline of the Core Study.

* Number of patients considered treatment responders, defined as those with a

*25%, *50%, *75%, or 100% reduction in convulsive seizures, relative to the pre-randomization baseline of the Core Study.

* Number of patients experiencing a >25% worsening, *25 to +25% no change, 25* 50% improvement, 50*75% improvement or >75% improvement in convulsive seizures, relative to the pre-randomization baseline of the Core Study.

LGS Patients Only:

* Percentage change in the number of drop seizures, relative to the pre-randomization baseline of the Core Study.

* Percentage change in the number of non-drop seizures, relative to the pre-randomization baseline of the Core Study.

* Number of patients considered treatment responders, defined as those with a *25%, *50%, *75%, or 100% reduction in drop seizures, relative to the pre-randomization baseline of the Core Study.

* Number of patients experiencing a >25% worsening, *25 to +25% no change, 25* 50% improvement, 50*75% improvement or >75% improvement in drop seizures, relative to the pre-randomization baseline of the Core Study.

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 patient (8.3%) achieving complete seizure freedom. The only 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

To evaluate the long term safety and tolerability of GWP42003-P, as adjunctive treatment, in children and adults with inadequately controlled DS or LGS.

All Patients:
To evaluate the effect of GWP42003-P, as adjunctive treatment, on:
* Quality of life.
* Adaptive behavior.
* Need for hospitalizations due to epilepsy.
* Usage of rescue medication.
* Maintenance of seizure frequency reduction and freedom from seizures during the open label extension (OLE) study.
* Frequency of total and subtypes of seizures.
* Change in duration of subtypes of seizures.
* Number of episodes of status epilepticus.
* Cognitive function.
* Growth and development.
* Menstruation cycles (in females).
* Signals indicating drug abuse liability of GWP42003-P.

DS Patients Only:
To evaluate the effect of GWP42003-P, as adjunctive treatment, on:
* Total convulsive seizure frequency.
* Total non-convulsive seizure frequency.
* Number of patients convulsive seizure free.
* Responder rate (defined in terms of percentage reduction in total convulsive seizure frequency).

LGS Patients Only:
To evaluate the effect of GWP42003-P, as adjunctive treatment, on:
* Drop seizure frequency.
* Non-drop seizure frequency.
* Number of patients drop seizure free.
* Responder rate (defined in terms of percentage reduction in drop seizure frequency).

Study design

This is a multi-center, OLE study for patients with DS or LGS who have completed the double-blind, placebo-controlled, clinical studies with GWP42003-P (Core Studies). The study consists of a titration period and a

maintenance period, followed by a 10-day taper period.

Titration Period: All patients will titrate up to 10-20 mg/kg/day GWP42003-P using a recommendend titration schedule.

It is advised that the Investigator considers monitoring hepatic function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin [TBL] and international normalized ratio [INR] levels) during the titration period for patients taking concomitant antiepileptic drugs (AEDs) that are known to be associated with hepatic injury or failure. To minimize any elevations in hepatic function markers the titration period can be extended and the dosage of a concomitant AED and/or GWP42003-P may be adjusted at the discretion of the Investigator. If there is intolerance during titration, the patient may be maintained on a dose below 10*20 mg/kg/day. A titration rate faster than recommended may be considered if there is an increase in seizures, following consultation with the GW Research Ltd (GW) medical monitor.

Maintenance Period: Patients will continue dosing at doses up to 10-20 mg/kg/day. However, investigators may decrease the dose if a patient experiences intolerance, or increase the dose if required for better seizure control, until the optimal dose is found. The investigator may schedule additional clinic visits to facilitate dose adjustments, e.g. when increasing doses above 20 mg/kg/day. Patients whose dose has been decreased can have their dose increased again provided there is adequate tolerance. The maximum dose patients can receive will be 30 mg/kg/day (51 mg/kg/day is the maximum dose safely used in the USA Intermediate Expanded Access Investigational New Drug program (EAP) to date, with a mean dose of 24 mg/kg/day [n=59]). Dose increases above 20 mg/kg/day are recommended to be done slowly, with maximum increments of 2.5 mg/kg every 5 - 7 days. If seizure freedom is achieved with use of GWP42003-P during the study, the investigator can consider reducing the dose of concomitant AEDs after consultation with the GW medical monitor.

Study Completion: The duration of this OLE study will be a maximum of 1 year (48 weeks after Visit 1). Patients who do not immediately continue to use GWP42003-P will then commence a taper period (down-titrating 10% per day for 10 days) and complete an *End of Taper Period* visit followed by a Follow-up visit (which can be by telephone) 4 weeks later.
If a patient opts not to continue with GWP42003-P treatment they will commence the 10-day taper period and complete the *End of Taper Period* visit and the Follow-up visit.
If supported by the safety data, the sponsor will look to extend the duration of this study .

Interim Analysis: At least 1 interim analysis will be conducted, approximately 6 months after the first patient first dose, to support New Drug Application and Marketing Authorization Application filings. Further interim analysis may

be conducted as required.

Intervention

GWP42003-P oral solution (100 mg/mL CBD in sesame oil with anhydrous ethanol, added sweetener [sucralose] and strawberry flavoring).
Dosage: Patients will titrate up to 10-20 mg/kg/day GWP42003-P. Patients will then remain at this dose until the *End of Treatment* visit, with the option for doses to be increased (up to 30 mg/kg/day, maximum) or decreased, if deemed necessary by the investigator. Following the *End of Treatment/Withdrawal visit', doses of IMP will be down-titrated at home (10% per day for 10 days) until the *End of Taper Period* visit.
IMP will be taken twice daily (morning and evening).

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)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

* Patient has completed the treatment phase of their Core Study.;* Patient and/or parent(s)/legal representative must be willing and able to give informed consent/assent 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 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

* Patient is currently using or has in the past used recreational or medicinal cannabis, or synthetic cannabinoid-based medications (including Sativex®) within the 3 months prior to study entry, not including IMP received during the Core study.
* 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.
* Any history of suicidal behavior or any suicidal ideation of type 4 or 5 on the C-SSRS at Visit 1.
* Patient has been part of a clinical trial involving an IMP during the inter-study period.
* Patient has previously been enrolled and dosed in this study.
* 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 3 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 3 months thereafter.
* 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.
* 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.
* Patient has significantly impaired hepatic function at the *End of Treatment* visit of their Core Study or at Visit 1 if re-assessed, defined as any of the following:
* ALT or AST > 5 × upper limit of normal (ULN).
* ALT or AST > 3 × ULN and (TBL > 2 × ULN or 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%).

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-10-2015
Enrollment:	40
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	18-06-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-09-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-05-2016

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-05-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-08-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-08-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-09-2017

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-12-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-02-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-01-2020
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	EUCTR2014-001834-27-NL
ClinicalTrials.gov	NCT02224573
CCMO	NL50883.041.15

Study results

Results posted: 09-04-2021

First publication
08-04-2021