A phase 2, double-blind, randomized, placebo-controlled pharmacokinetic trial in two parallel groups to investigate possible drug- drug interactions between stiripentol or valproate and GWP42003-P in patients with epilepsy.

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Primary ObjectiveTo determine whether GWP42003-P affects the pharmacokinetic (PK) profile of stiripentol (STP) or valproate (VPA).Secondary Objective(s)To assess the safety and tolerability of GWP42003-P in the presence of STP or VPA.

Ethical review	Not approved
Status	Will not start
Health condition type	Seizures (incl subtypes)
Study type	Interventional

Summary

ID

NL-OMON42499

Source
ToetsingOnline

Brief title
GWEP1447

Condition

- Seizures (incl subtypes)

Synonym
epilepsy

Research involving

Human

Sponsors and support

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

Intervention

Keyword: cannabidiol, epilepsy

Outcome measures

Primary outcome

The primary endpoints of the trial are the PK parameters (Cmax, tmax, AUC(0**),

AUC(0*t) and t*) of the following analytes:

* STP

* VPA

* CBD

* CBD major metabolites

Secondary outcome

To assess the safety and tolerability of GWP42003-P compared with placebo when

taken in combination with STP or VPA. Safety and tolerability will be assessed

using the following parameters:

* AEs

* 12-lead electrocardiogram (ECG)

* Clinical laboratory parameters (biochemistry, hematology and urinalysis)

* Physical examination

* Vital signs

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

* Seizure frequency

* Abuse liability

* CYP2C19 and CPY3A4 patient genotype analysis

* 2-propyl-4-pentenoic acid (4-ene-VPA)

PK parameters (Cmax, tmax, AUC(0**) AUC(0*t) and t*) of the following analytes:

* THC

* THC major metabolites

Study description

Background summary

CYP450 enzymes are a family of heme-containing enzymes responsible for the metabolism of over half of all prescribed medications, and interactions with these enzymes are the major source of physiologically-based pharmacokinetic (PBPK) interactions between drugs. It is anticipated that patients taking GWP42003-P may also be taking VPA or STP, and as CBD has been shown to both inhibit CYP450 enzymes in vitro (Ki CYP3A4 = 1.5 *M) and induce CYP450 enzymes in vitro (EC50 CYP3A4 = 1.2 *g/mL), a possibility of a PK interaction between GWP42003-P and VPA or STP exists. Given the high likelihood that patients prescribed GWP42003-P will also be using VPA or STP, it is the aim and purpose of this trial to determine whether a PK interaction between GWP42003-P, STP and VPA exists.

CBD can act as both a CYP inhibitor and inducer in human hepatocytes in vitro. Therefore, the potential for PK interactions with other drugs that are metabolized by CYP450 enzymes exists. The hypothesis is that the in vivo PK of STP or VPA may be altered (increased or decreased) by the chronic administration of GWP42003-P.

Study objective

Primary Objective
To determine whether GWP42003-P affects the pharmacokinetic (PK) profile of stiripentol (STP) or valproate (VPA).
Secondary Objective(s)
To assess the safety and tolerability of GWP42003-P in the presence of STP or

VPA.

Study design

This is a phase 2, double-blind, randomized, placebo-controlled PK trial in two parallel groups in 40 patients.
* Patients will enter either the STP or VPA arms and will be randomized in a 4:1 ratio to receive either 20 mg/kg GWP42003-P or placebo from Days 2 to 26.
* At the end of the treatment period, patients will be given the option of continuing onto an open label extension (OLE) period if the investigator and patient both agree that it is in their best interests. Doses may be adjusted up or down, at the investigator*s discretion, to a maximum of 30 mg/kg/day GWP42003-P. The OLE period will last for a maximum of one year or until marketing authorization is granted; whichever is earlier.
* Patients that do not continue onto the OLE period will taper off GWP42003-P over a 10 day period and will have a telephone follow-up visit four weeks after the end of taper day on Day 64.
* Day 1 (Visit 2): patients will not be dosed with investigational medicinal product (IMP) (GWP42003-P or placebo) but will continue to take STP or VPA at a stable dose.
* Day 2 (Visit 2): patients will begin the up-titration with GWP42003-P or placebo to a maintenance dose or an equivalent maintenance dose of 20 mg/kg/day over a period of 10 days (Days 2 to 11).
* Day 12 (Visit 3): patients will attend the study site to check safety and compliance.
* After up-titration with GWP42003-P or placebo, the patients will remain on the maintenance dose for 14 days (Days 12 to 25) before coming in for the next PK visit on Day 26.
* On Day 27 (Visit 4), patients will be invited to receive GWP42003-P in the OLE period. If the patient enters the OLE period of the trial, the patient will continue to take GWP42003-P as advised by the investigator.
* If the patient does not enter the OLE period of the trial, the patient will taper off GWP42003-P by reducing the dose by approximately 10% of the maintenance dose each day until dosing has ceased, with an End of Taper visit on Day 36 (Visit 5) and a safety follow-up telephone call four weeks after the end of taper, on Day 64.

PK samples will be taken on the day of enrollment (Visit 2, Days 1 and 2) and after completing 14 days treatment on GWP42003-P or placebo (Visit 4, Days 26 and 27). The PK assessments will therefore capture the following combinations of STP, VPA and IMP:
* First PK assessment: STP or VPA alone.
* Second PK assessment: STP or VPA in combination with GWP42003-P/placebo.

Each PK assessment should be performed at time-points in respect to a morning dose of STP or VPA. The time-points are as follows: Pre-dose, 15 and 30 minutes, then 1, 1.5, 2, 4, 6, 12 and 24 hours post-dose. It is expected that

the patient will continue to take their STP or VPA as advised by their physician and PK assessments will be scheduled in order to accommodate this dosing schedule. The GWP42003-P/placebo should be taken twice daily immediately following the STP or VPA doses.

PK assessments will analyze plasma levels of STP or VPA, cannabidiol (CBD), CBD major metabolites, *9-tetrahydrocannabinol (THC), THC major metabolites, Clobazam (CLB), N-desmethylclobazam (N-CLB), Levetiracetam (LEV) and Topiramate (TPM).
Patients will be required to keep a paper diary to note the time and dose of IMP and STP or VPA administration each morning and evening, and to record any adverse events (AEs) that may occur whilst receiving IMP and any other medications. Patients will also be requested to record the number and type of seizures experienced each day whilst on the trial.

Intervention

A total of 40 patients will be enrolled in this trial (20 patients in the STP arm and 20 in the VPA arm). Patients will enter either the STP or VPA arms and will be randomized in a 4:1 ratio to receive either 20 mg/kg GWP42003-P or placebo.

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)
Elderly (65 years and older)

Inclusion criteria

For inclusion in the trial patients must fulfil ALL of the following criteria:;6.1.1 Male or female

patients aged 16 to 55 years inclusive.;6.1.2 Patient must be taking STP (for the STP arm) or VPA (for the VPA arm) and no more than two other AEDs during the blinded period of the trial.;- In the VPA arm only, the patient must not be receiving STP (VPA allowed in STP arm).;6.1.3 AED doses, including STP or VPA, must be stable for four weeks prior to screening and regimen must remain stable throughout the duration of the blinded period of the trial.;6.1.4 Patient must have a documented magnetic resonance imaging/computerized tomography of the brain that ruled out a progressive neurologic condition.;6.1.5 Patient must have experienced at least one countable uncontrolled seizures of any type (i.e., tonic-clonic, tonic, clonic, atonic, partial onset or focal: focal seizures with retained consciousness and a motor component, focal seizures with impaired consciousness, focal seizures evolving to bilateral secondary generalization) within two months prior to randomization.;6.1.6 Intervention with vagus nerve stimulation (VNS) and/or ketogenic diet must be stable for four weeks prior to baseline and the patient must be willing to maintain a stable regimen during the blinded period of the trial.;6.1.7 Patients must abstain from alcohol during the blinded period of the trial.;6.1.8 Patient and legal representative (if required) is available to attend all PK visits within the required visit window.;6.1.9 Patient and legal representative (if required) must be willing and able to give informed consent/assent for participation in the trial.;6.1.10 Patient must be willing and able (in the investigator*s opinion) to comply with all trial requirements.;6.1.11 Patient is willing for his or her name to be notified to the responsible authorities for participation in this trial, as applicable.;6.1.12 Patient is willing to allow his or her primary care practitioner and consultant, if appropriate, to be notified of participation in the trial.

Exclusion criteria

The patient may not enter the trial if ANY of the following apply:;6.2.1 Patient has clinically significant unstable medical conditions other than epilepsy.;6.2.2 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 (orthostatic blood pressure changes).;6.2.3 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.;6.2.4 Patient has had clinically relevant symptoms or a clinically significant illness in the four weeks prior to screening or enrollment, other than epilepsy.;6.2.5 Patient is currently using Felbamate and has been taking it for less than 12 months prior to screening.;6.2.6 Patient has consumed alcohol during the seven days prior to enrollment and is unwilling to abstain during the blinded period of the trial.;6.2.7 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 trial entry or is unwilling to abstain for the duration of the trial.;6.2.8 Patient has any known or suspected history of any drug abuse or addiction.;6.2.9 Patient has consumed grapefruit or grapefruit juice seven days prior to enrollment and is unwilling to abstain from drinking or eating grapefruit within seven days of PK visits.;6.2.10 Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, e.g., sesame oil.;6.2.11 Female patient of child bearing potential, or male patient*s partner is of child bearing potential, unless willing to ensure that they or their partner use a highly effective method of birth control (e.g., hormonal contraceptives, intrauterine devices/hormone-

releasing systems, bilateral tubal occlusion, vasectomized partner, sexual abstinence) during the trial and for three months thereafter.;6.2.12 Female patient who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the trial and for three months thereafter.;6.2.13 Patient who has received an IMP within the 12 weeks prior to the screening visit.;6.2.14 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 trial, may influence the result of the trial, or the patient*s ability to participate in the trial.;6.2.15 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 trial.;6.2.16 Patient has significantly impaired hepatic function, as determined at screening (Visit 1) or enrollment (Visit 2) defined as any of the following:;- Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST);>5 × upper limit of normal (ULN).;- ALT or AST >3 x ULN and (total bilirubin [TBL] >2 × ULN or;international normalized ratio [INR] >1.5).;- ALT or AST >3 x ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).;This criterion can only be confirmed once the laboratory results are available; patients randomized into the trial who are later found to meet this screening criterion must be withdrawn from the trial.;6.2.17 Unwilling to abstain from donation of blood during the trial.;6.2.18 Patient has travel outside the country of residence planned during the trial, unless the patient has confirmation that the IMP is permitted in the destination country/state.;6.2.19 Patients previously enrolled into any GWP42003-P trial.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Convulex
Generic name:	Valproate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Diacomet
Generic name:	Stiripentol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Epidiolex
Generic name:	canabidiol

Ethics review

Not approved Date:	25-01-2016
Application type:	First submission
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	EUCTR2015-002939-18-NL

Register	ID
ClinicalTrials.gov	NCT02607891/NCT02607904
CCMO	NL55983.041.15