A 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 (GWPCARE4)

ClinicalTrials.gov Identifier: NCT02224690

Recruitment Status : Completed
First Posted : August 25, 2014
Results First Posted : July 27, 2018
Last Update Posted : July 27, 2018

Sponsor:
GW Research Ltd

Information provided by (Responsible Party):
GW Research Ltd

Study Description

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Brief Summary:
To evaluate the efficacy of GWP42003-P as adjunctive treatment in reducing the number of drop seizures when compared with placebo, in participants with Lennox-Gastaut Syndrome (LGS).

Condition or disease	Intervention/treatment	Phase
Epilepsy Lennox-Gastaut Syndrome	Drug: GWP42003-P 20 mg/kg/day Dose Drug: Placebo	Phase 3

Detailed Description:
This study was a 1:1 randomized, double-blind, 14-week comparison of 20 milligram [mg] per kilogram [kg] per day [mg/kg/day] of GWP42003-P versus placebo. The treatment period consisted of a 2-week titration period followed by a 12-week maintenance period. The study determined the efficacy, safety and tolerability of GWP42003-P compared with placebo. The dose was recommended by the Data Safety Monitoring Committee (DSMC) after assessment of safety and pharmacokinetic data from Part A of study GWEP1332. The first participants enrolled into this study after the DSMC reviewed the safety data from Part A of study GWEP1332. Following study completion, all participants were invited to continue to receive GWP42003-P in an open label extension (OLE) study (under a separate protocol).

Study Design

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Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	171 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	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.
Actual Study Start Date :	April 28, 2015
Actual Primary Completion Date :	March 18, 2016
Actual Study Completion Date :	March 18, 2016

Resource links provided by the National Library of Medicine

Genetics Home Reference related topics: Lennox-Gastaut syndrome Pyridoxal 5'-phosphate-dependent epilepsy

MedlinePlus related topics: Seizures

Genetic and Rare Diseases Information Center resources: Lennox-Gastaut Syndrome

U.S. FDA Resources

Arms and Interventions

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Arm	Intervention/treatment
Experimental: GWP42003-P 20 mg/kg/day Dose Participants received GWP42003-P 20 mg/kg/day administered orally, half in the morning and half in the evening. Participants titrated GWP42003-P to 20 mg/kg/day over 11 days and remained at this dose for the 12-week maintenance period. If the participant did not immediately enter the OLE study, the maintenance period was followed by a 10-day taper (10% per day) period.	Drug: GWP42003-P 20 mg/kg/day Dose GWP42003-P was presented as an oral solution containing 100 mg/milliliter (mL) cannabidiol (CBD) in the excipients sesame oil and anhydrous ethanol (79 mg/mL) with added sweetener (0.5 mg/mL sucralose) and strawberry flavoring (0.2 mg/mL). Other Names: • Cannabidiol • Epidiolex
Placebo Comparator: Placebo Participants received placebo (0 mg/mL CBD), volume matched to the 20 mg/kg/day dose, administered orally, half in the morning and half in the evening. To maintain the blinded aspect of the study, participants titrated the placebo dose over 11 days and remained at this dose for the 12-week maintenance period. If the participant did not immediately enter the OLE study, the maintenance period was followed by a 10-day taper (10% per day) period.	Drug: Placebo Placebo was presented as an oral solution containing 0 mg/mL CBD in the excipients sesame oil and anhydrous ethanol (79 mg/mL) with added sweetener (0.5 mg/mL sucralose) and strawberry flavoring (0.2 mg/mL).

Outcome Measures

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Primary Outcome Measures :

1. Percentage Change From Baseline In Drop Seizure Frequency During The Treatment Period [Time Frame: Baseline to End of Treatment (EOT) (Day 99) or Early Termination (ET)]

   Drop seizures were recorded by the participant or caregiver using an interactive voice response system (IVRS) diary. Drop seizures were defined as the subset of tonic-clonic, tonic or atonic seizures that were reported as drop seizures in the IVRS. Percentage change from baseline was calculated as: (frequency during the treatment period - frequency during baseline/frequency during baseline) * 100. The frequency during each period was based on 28-day averages and calculated as: (number of seizures in the period/number of reported days in the IVRS period) *28. Baseline included all available data prior to Day 1 (28-day average). Negative percentages show an improvement from baseline.

Secondary Outcome Measures :

1. Number Of Participants With a ≥50% Reduction From Baseline in Drop Seizure Frequency During The Treatment Period [Time Frame: Baseline to EOT (Day 99) or ET]

   Drop seizures were recorded by the participant or caregiver using an IVRS diary. Drop seizures included the subset of tonic-clonic, tonic or atonic seizures that were reported as drop seizures in IVRS. Percentage change from baseline was calculated as per the primary outcome measure.

2. Percentage Change From Baseline In Total Seizure Frequency During The Treatment Period [Time Frame: Baseline to EOT (Day 99) or ET]

   Total seizures included the sum of all seizures (tonic-clonic, tonic, atonic, clonic, myoclonic, countable partial, other partial and absence seizures) recorded by the participant or caregiver using an IVRS diary. Percentage change from baseline was calculated as per the primary outcome measure. Negative percentages show an improvement from baseline.

3. Subject/Caregiver Global Impression Of Change Assessment (S/CGIC) [Time Frame: Baseline to Last Visit (Day 99) or ET]

   The S/CGIC was used to assess the participant's overall condition on a 7-point scale, using the markers "very much improved, much improved, slightly improved, no change, slightly worse, much worse, or very much worse" (1 = very much improved; 7 = very much worse). On Day 1 (prior to starting IMP), the caregiver was asked to write a brief description of the participant's overall condition as a memory aid for the S/CGIC questionnaire at subsequent visits. If both a CGIC and SGIC were completed then the CGIC was used; if only a CGIC was completed then the CGIC was used; if only a SGIC was completed then the SGIC was used. Last visit for endpoints assessed at clinic visits was defined as the last scheduled visit (not including the end of taper or safety follow-up visits) at which participant's last evaluation was performed.

Eligibility Criteria

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Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	2 Years to 55 Years (Child, Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Key Inclusion Criteria:

- Participant must have been male or female aged between 2 and 55 years (inclusive).
- Participant must have had a documented history of Lennox-Gastaut syndrome. This included written documentation of having met electroencephalogram (EEG) diagnostic criteria during the participant's history and evidence of at least 1 type of generalized seizure, including drop seizures (atonic, tonic, tonic-clonic or myoclonic) for at least 6 months.
- Participants had a history of slow (<3.0 Hertz) spike-and-wave pattern in an EEG prior to the enrollment into the baseline period.
- Participants were refractory; that is having documented failures on more than one antiepileptic drug (AED).
- Participant must have been taking 1 or more AEDs at a dose which has been stable for at least 4 weeks prior to screening.
- All medications or interventions for epilepsy (including ketogenic diet and vagus nerve stimulation [VNS]) must have been stable for 4 weeks prior to screening and participant is willing to maintain a stable regimen throughout the study. The ketogenic diet and VNS treatments are not accounted as an AED.

Key Exclusion Criteria:

- Etiology of participant's seizures was a progressive neurologic disease. Participants with tuberous sclerosis were not excluded from study participation, unless there was a progressive tumor.
- Participant had an anoxic episode requiring resuscitation within 6 months of screening.
- Participant had clinically significant unstable medical conditions other than epilepsy.
- Participant had clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to screening or randomization, other than epilepsy.
- Participant was 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 and was unwilling to abstain for the duration of the study.
- Participant had any known or suspected hypersensitivity to cannabinoids or any of the excipients of the Investigational Medicinal Product (IMP), such as sesame oil.
- Participant had been part of a clinical trial involving another IMP in the previous 6 months.
- Participant had significantly impaired hepatic function at screening or randomization (Alanine aminotransferase [ALT] >5 x upper limit of normal [ULN] or 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 >1.5). This criterion can only be confirmed once the laboratory results are available; Participants randomized into the study who are later found not to meet this criterion should be withdrawn from the study.
- Any history of suicidal behavior or any suicidal ideation of type 4 or 5 on the Columbia Suicide Severity Rating Scale in the last month or at screening.
- Participant was taking more than 4 concurrent AEDs.
- Participant was taking corticotropins in the 6 months prior to screening.
- Participant was taking long-term systemic steroids (excluding inhaled medication for asthma treatment) or any other daily medication known to exacerbate epilepsy. An exception was made of prophylactic medication, for example, idiopathic nephrotic syndrome or asthma.
- Participant was taking felbamate, and they had been taking it for less than 1 year prior to screening.

Contacts and Locations

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Information from the National Library of Medicine

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

*Please refer to this study by its ClinicalTrials.gov identifier (NCT number): **NCT02224690***

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Sponsors and Collaborators

GW Research Ltd

More Information

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Publications:

Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, Lyons PD, Taylor A, Roberts C, Sommerville K; GWPCARE4 Study Group. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018 Mar 17;391(10125):1085-1096. doi: 10.1016/S0140-6736(18)30136-3. Epub 2018 Jan 26.

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Keywords provided by GW Research Ltd:
Cannabidiol
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Additional relevant MeSH terms:

Syndrome	Brain Diseases
Seizures	Central Nervous System Diseases
Lennox Gastaut Syndrome	Nervous System Diseases
Disease	Neurologic Manifestations
Pathologic Processes	Signs and Symptoms
Epilepsy	Genetic Diseases, Inborn