Clinical trial results:
A phase 2, double-blind, randomized, placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P).

Summary

EudraCT number	2014-002942-33
Trial protocol	GB ES
Global end of trial date	07 June 2017

Results information

Result version number	v1 (current)
This version publication date	06 October 2018
First version publication date	06 October 2018

Trial information

Trial identification

Sponsor protocol code	GWEP1428

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02565108
WHO universal trial number (UTN)	-
Other trial identifiers	NCT02565108: NCT number for GWEP1428 Blinded Phase, NCT02564952: NCT Number for GWEP1428 Open-Label Extension

Notes:

Sponsors

Sponsor organisation name	GW Research Ltd
Sponsor organisation address	Sovereign House, Vision Park, Chivers Way, Histon, Cambridge, United Kingdom, CB24 9BZ
Public contact	Alternate contact: medinfo@greenwichbiosciences.com, GW Research Ltd, medinfo@gwpharm.com
Scientific contact	Alternate contact: medinfo@greenwichbiosciences.com, GW Research Ltd, medinfo@gwpharm.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 June 2017
Global end of trial reached?	Yes
Global end of trial date	07 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Period 1 (Double-Blind [DB] Phase):
To determine whether GWP42003-P affects the pharmacokinetic (PK) profile of clobazam (CLB) and its primary metabolite N-desmethylclobazam (N-CLB). The primary completion date for the DB phase was 21-July-2016.

Period 2 (Open-Label [OLE] Phase):
To assess the long-term safety and tolerability of GWP42003-P in participants with epilepsy.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which the study was conducted. No study procedures were performed on study candidates until written consent had been obtained from the participant. The informed consent form, protocol, and amendments for this study were submitted to and approved by the institutional review board or independent ethics committee at each participating study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 10
Worldwide total number of subjects	20
EEA total number of subjects	20

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	20
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants had been clinically diagnosed with epilepsy and had been taking CLB and no more than 2 other antiepileptic drugs (AEDs) during the course of the study. Participant must have experienced at least 1 seizure of any type within the 2 months prior to randomization.

Period 1

Period 1 title	Double-Blind (BL, trtmt, follow-up)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Period 1: GWP42003-P

Arm description:

Participants received GWP42003-P 20 milligram (mg)/kilogram (kg)/day orally, twice daily immediately after their CLB dose. Participants titrated GWP42003-P to 20 mg/kg/day over 10 days and remained at this dose for the 21-day treatment period. Participants who then did not enter the OLE or withdrew early had a 10-day taper (10% per day) period. Participants who transferred to the OLE (still blinded at that stage) tapered off their GWP42003-P treatment by reducing their maintenance dose by 10% per day and concomitantly titrating GWP42003-P for the OLE.

All participants (in the GWP42003-P and Placebo treatment groups) were on a stable dose of CLB at Baseline, administered either once or twice daily as per the physician's preferred CLB dosing regimen for each participant, and continued taking CLB, as an Investigational Medicinal Product (IMP), for the duration of this study.

Arm type	Experimental
Investigational medicinal product name	GWP42003-P
Investigational medicinal product code	GWP42003-P
Other name	Epidiolex, Cannabidiol, CBD
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

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).

Arm title	Period 1: Placebo

Arm description:

Participants received placebo (0 mg/mL GWP42003-P) orally, twice daily immediately after the participant's CLB dose. Participants titrated the placebo dose over 10 days, followed by a 21-day treatment period. Participants who then did not enter the OLE or withdrew early had a 10-day taper (10% per day) period. Participants who transferred to the OLE (still blinded at that stage) tapered off their placebo treatment by reducing their maintenance dose by 10% per day and concomitantly titrating GWP42003-P for the OLE.

All participants (in the GWP42003-P and Placebo treatment groups) were on a stable dose of CLB at Baseline, administered either once or twice daily as per the physician's preferred CLB dosing regimen for each participant, and continued taking CLB, as an IMP, for the duration of this study.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo control
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

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).

Number of subjects in period 1	Period 1: GWP42003-P	Period 1: Placebo
Started	16	4
PK Set	10 [1]	3 [2]
Safety Set	16	4
Completed	14	4
Not completed	2	0
Withdrew Consent	1	-
Adverse event, non-fatal	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The GWP42003-P group had 16 participants start and 14 participants who completed the study. Of the 2 who did not complete the study, 1 withdrew consent and 1 was withdrawn from the study by the investigator due to a serious AE. The Safety Set included all 16 participants. The PK set included 10 participants (6 were excluded due to GWP42003-P and/or CLB dose modification, GWP42003-P or placebo discontinuation, discontinuation from the study, or incorrect dose administration).
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: There were 4 participants who started in the Placebo group, and 4 who completed the study. The Safety Set included all 4 participants. The PK set included 3 participants; 1 participant was excluded from the PK set because placebo was administered on Day 1, after predose sampling.

Period 2

Period 2 title	Open-Label Extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Period 2: GWP42003-P

Arm description:

Participants who transferred from the DB phase to the OLE (still blinded at that stage) tapered off their GWP42003-P or placebo treatment by reducing their maintenance dose by 10% per day and concomitantly titrating GWP42003-P to 20 mg/kg/day initially for the OLE; doses could then be adjusted up or down, dependent on investigator opinion, to a maximum of 30 mg/kg/day GWP42003-P.

Participants were taking CLB upon entry into the OLE phase of the trial. CLB was not an IMP for the OLE phase and was not administered by the Sponsor. CLB was administered in line with the physician's preferred CLB dosing regimen for each participant. CLB could be stopped, if clinically indicated, without impact on analysis.

Arm type	Experimental
Investigational medicinal product name	GWP42003-P up to a maximum of 30 mg/kg/day dose
Investigational medicinal product code	GWP42003-P
Other name	Epidiolex, Cannabidiol, CBD
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

GWP42003-P was presented as an oral solution containing 100 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).

Number of subjects in period 2	Period 2: GWP42003-P
Started	18
Received at Least 1 Dose of Study Drug	18
Completed OLE Titration Period	16
Completed	7
Not completed	11
Withdrawal by Participant	1
Adverse Event	6
Participant Withdrawn by Investigator	1
Participant Met Withdrawal Criteria	1
Low efficacy	1
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	Period 1: GWP42003-P

Reporting group description:

Participants received GWP42003-P 20 milligram (mg)/kilogram (kg)/day orally, twice daily immediately after their CLB dose. Participants titrated GWP42003-P to 20 mg/kg/day over 10 days and remained at this dose for the 21-day treatment period. Participants who then did not enter the OLE or withdrew early had a 10-day taper (10% per day) period. Participants who transferred to the OLE (still blinded at that stage) tapered off their GWP42003-P treatment by reducing their maintenance dose by 10% per day and concomitantly titrating GWP42003-P for the OLE.

All participants (in the GWP42003-P and Placebo treatment groups) were on a stable dose of CLB at Baseline, administered either once or twice daily as per the physician's preferred CLB dosing regimen for each participant, and continued taking CLB, as an Investigational Medicinal Product (IMP), for the duration of this study.

Reporting group title	Period 1: Placebo

Reporting group description:

Participants received placebo (0 mg/mL GWP42003-P) orally, twice daily immediately after the participant's CLB dose. Participants titrated the placebo dose over 10 days, followed by a 21-day treatment period. Participants who then did not enter the OLE or withdrew early had a 10-day taper (10% per day) period. Participants who transferred to the OLE (still blinded at that stage) tapered off their placebo treatment by reducing their maintenance dose by 10% per day and concomitantly titrating GWP42003-P for the OLE.

All participants (in the GWP42003-P and Placebo treatment groups) were on a stable dose of CLB at Baseline, administered either once or twice daily as per the physician's preferred CLB dosing regimen for each participant, and continued taking CLB, as an IMP, for the duration of this study.

Reporting group values	Period 1: GWP42003-P	Period 1: Placebo	Total
Number of subjects	16	4	20
Age categorical Units: Subjects			
Adults (18-64 years)	16	4	20
Age continuous Units: years			
arithmetic mean	36.60	37.57	
standard deviation	± 8.51	± 10.67	-
Gender categorical Units: Subjects			
Female	8	2	10
Male	8	2	10

Subject analysis sets

Subject analysis set title	Safety Set
Subject analysis set type	Full analysis

Subject analysis set description:

The safety set included all participants who received a dose of GWP42003-P or placebo.

Reporting group values	Safety Set		
Number of subjects	20		
Age categorical Units: Subjects			
Adults (18-64 years)	20		
Age continuous Units: years			
arithmetic mean	36.79		
standard deviation	± 8.68		
Gender categorical Units: Subjects			
Female	10		
Male	10		

End points reporting groups

Reporting group title	Period 1: GWP42003-P

Reporting group description:

Participants received GWP42003-P 20 milligram (mg)/kilogram (kg)/day orally, twice daily immediately after their CLB dose. Participants titrated GWP42003-P to 20 mg/kg/day over 10 days and remained at this dose for the 21-day treatment period. Participants who then did not enter the OLE or withdrew early had a 10-day taper (10% per day) period. Participants who transferred to the OLE (still blinded at that stage) tapered off their GWP42003-P treatment by reducing their maintenance dose by 10% per day and concomitantly titrating GWP42003-P for the OLE.

All participants (in the GWP42003-P and Placebo treatment groups) were on a stable dose of CLB at Baseline, administered either once or twice daily as per the physician's preferred CLB dosing regimen for each participant, and continued taking CLB, as an Investigational Medicinal Product (IMP), for the duration of this study.

Reporting group title	Period 1: Placebo

Reporting group description:

Participants received placebo (0 mg/mL GWP42003-P) orally, twice daily immediately after the participant's CLB dose. Participants titrated the placebo dose over 10 days, followed by a 21-day treatment period. Participants who then did not enter the OLE or withdrew early had a 10-day taper (10% per day) period. Participants who transferred to the OLE (still blinded at that stage) tapered off their placebo treatment by reducing their maintenance dose by 10% per day and concomitantly titrating GWP42003-P for the OLE.

All participants (in the GWP42003-P and Placebo treatment groups) were on a stable dose of CLB at Baseline, administered either once or twice daily as per the physician's preferred CLB dosing regimen for each participant, and continued taking CLB, as an IMP, for the duration of this study.

Reporting group title	Period 2: GWP42003-P

Reporting group description:

Participants who transferred from the DB phase to the OLE (still blinded at that stage) tapered off their GWP42003-P or placebo treatment by reducing their maintenance dose by 10% per day and concomitantly titrating GWP42003-P to 20 mg/kg/day initially for the OLE; doses could then be adjusted up or down, dependent on investigator opinion, to a maximum of 30 mg/kg/day GWP42003-P.

Participants were taking CLB upon entry into the OLE phase of the trial. CLB was not an IMP for the OLE phase and was not administered by the Sponsor. CLB was administered in line with the physician's preferred CLB dosing regimen for each participant. CLB could be stopped, if clinically indicated, without impact on analysis.

Subject analysis set title	Safety Set
Subject analysis set type	Full analysis

Subject analysis set description:

The safety set included all participants who received a dose of GWP42003-P or placebo.

Primary: Period 1: PK: Maximum Measured Plasma Concentration (Cmax) Of CLB And N-CLB With GWP42003-P Treatment, Days 1 And 33

End point title	Period 1: PK: Maximum Measured Plasma Concentration (Cmax) Of CLB And N-CLB With GWP42003-P Treatment, Days 1 And 33[1]

End point description:

The Cmax of CLB and its primary metabolite, N-CLB, was measured on Day 1 (before first GWP42003-P dose; participants were taking CLB only) and Day 33 (following 21 days of GWP42003-P or placebo maintenance treatment; participants were taking CLB and GWP42003-P or CLB and placebo). PK samples were taken at time points relative to the morning dose of CLB: Predose, 15 minutes (min), 30 min, 1 hour (h), 1.5 h, 2 h, 4 h, 6 h, 12 h, and 24 h.

PK Set: All participants who received at least 1 dose of GWP42003-P or placebo, who had not reduced their CLB dose between Day 1 and Day 33, and who provided some on-treatment data. One participant in the placebo group was excluded from the PK set because placebo was administered on Day 1, after predose sampling. Six participants in the GWP42003-P group were excluded from the PK set due to GWP42003-P and/or CLB dose modification, GWP42003-P or placebo discontinuation, discontinuation

from study, or incorrect dose administration.

End point type	Primary

End point timeframe:

Predose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 12, and 24 h postdose on Days 1 and 33

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Quantitative statistical analysis (for example, a p-value) was not performed for the PK endpoints. Descriptive statistics are included (geometric mean and % CV).

End point values	Period 1: GWP42003-P	Period 1: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: nanograms (ng)/mL				
geometric mean (geometric coefficient of variation)				
Day 1 CLB	330 (± 40.4)	440 (± 29.9)		
Day 33 CLB	329 (± 54.8)	461 (± 102.3)		
Day 1 N-CLB	2060 (± 138.4)	1130 (± 82.1)		
Day 33 N-CLB	4570 (± 54.0)	1320 (± 134.1)		
Day 1 CLB Dose-normalized	19.3 (± 31.4)	22.0 (± 29.9)		
Day 33 CLB Dose-normalized	19.2 (± 44.7)	23.1 (± 102.3)		
Day 1 N-CLB Dose-normalized	121 (± 125.1)	56.6 (± 82.1)		
Day 33 N-CLB Dose-normalized	267 (± 38.6)	66.1 (± 134.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Period 1: PK: Time To The Maximum Plasma Concentration (tmax) Of CLB And N-CLB With GWP42003-P Treatment, Days 1 And 33

End point title	Period 1: PK: Time To The Maximum Plasma Concentration (tmax) Of CLB And N-CLB With GWP42003-P Treatment, Days 1 And 33[2]

End point description:

The tmax of CLB and its primary metabolite, N-CLB, was measured on Day 1 (before first GWP42003-P dose; participants were taking CLB only) and Day 33 (following 21 days of GWP42003-P or placebo maintenance treatment; participants were taking CLB and GWP42003-P or CLB and placebo). PK samples were taken at time points relative to the morning dose of CLB: Predose, 15 min, 30 min, 1 h, 1.5 h, 2 h, 4 h, 6 h, 12 h, and 24 h.

PK Set: All participants who received at least 1 dose of GWP42003-P or placebo, who had not reduced their CLB dose between Day 1 and Day 33, and who provided some on-treatment data. One participant in the placebo group was excluded from the PK set because placebo was administered on Day 1, after predose sampling. Six participants in the GWP42003-P group were excluded from the PK set due to GWP42003-P and/or CLB dose modification, GWP42003-P or placebo discontinuation, discontinuation from study, or incorrect dose administration.

End point type	Primary

End point timeframe:

Predose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 12, and 24 h postdose on Days 1 and 33

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Quantitative statistical analysis (for example, a p-value) was not performed for the PK

endpoints. Descriptive statistics are included (median and range).

End point values	Period 1: GWP42003-P	Period 1: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: hours				
median (full range (min-max))				
Day 1 CLB	1.00 (0.8 to 4.0)	1.17 (1.0 to 1.5)		
Day 33 CLB	1.86 (0.5 to 4.0)	1.58 (1.5 to 2.0)		
Day 1 N-CLB	1.50 (0.3 to 6.0)	2.00 (0.0 to 12.0)		
Day 33 N-CLB	3.03 (0.0 to 11.1)	1.00 (0.3 to 2.0)		

Statistical analyses

No statistical analyses for this end point

Primary: Period 1: PK: Area Under The Plasma Concentration Time Curve Over A Dosing Interval, Where Tau Is The Dosing Interval (AUCtau) Of CLB And N-CLB With GWP42003-P Treatment, Days 1 And 33

End point title	Period 1: PK: Area Under The Plasma Concentration Time Curve Over A Dosing Interval, Where Tau Is The Dosing Interval (AUCtau) Of CLB And N-CLB With GWP42003-P Treatment, Days 1 And 33[3]

End point description:

The AUCtau of CLB and its primary metabolite, N-CLB, was measured on Day 1 (before first GWP42003-P dose; participants were taking CLB only) and Day 33 (following 21 days of GWP42003-P or placebo maintenance treatment; participants were taking CLB and GWP42003-P or CLB and placebo). PK samples were taken at time points relative to the morning dose of CLB: Predose, 15 min, 30 min, 1 h, 1.5 h, 2 h, 4 h, 6 h, 12 h, and 24 h.

PK Set: All participants who received at least 1 dose of GWP42003-P or placebo, who had not reduced their CLB dose between Day 1 and Day 33, and who provided some on-treatment data. One participant in the placebo group was excluded from the PK set because placebo was administered on Day 1, after predose sampling. Six participants in the GWP42003-P group were excluded from the PK set due to GWP42003-P and/or CLB dose modification, GWP42003-P or placebo discontinuation, discontinuation from study, or incorrect dose administration.

End point type	Primary

End point timeframe:

Predose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 12, and 24 h postdose on Days 1 and 33

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Quantitative statistical analysis (for example, a p-value) was not performed for the PK endpoints. Descriptive statistics are included (geometric mean and % CV).

End point values	Period 1: GWP42003-P	Period 1: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1 CLB	2690 (± 52.9)	3320 (± 67.5)		
Day 33 CLB	2840 (± 46.2)	3310 (± 102.5)		
Day 1 N-CLB	18300 (± 124.2)	11400 (± 63.7)		
Day 33 N-CLB	48400 (± 53.9)	11500 (± 79.1)		
Day 1 CLB Dose-normalized	157 (± 47.1)	166 (± 67.5)		
Day 33 CLB Dose-normalized	166 (± 34.7)	165 (± 102.5)		
Day 1 N-CLB Dose-normalized	1070 (± 105.1)	571 (± 63.7)		
Day 33 N-CLB Dose-normalized	2830 (± 38.3)	573 (± 79.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Period 1: PK: Geometric Mean Ratios Of CLB And N-CLB For Cmax On Day 33 Compared With Day 1

End point title	Period 1: PK: Geometric Mean Ratios Of CLB And N-CLB For Cmax On Day 33 Compared With Day 1[4]

End point description:

The Day 33 compared to Day 1 geometric mean ratios of CLB and N-CLB were calculated for Cmax to look for evidence of drug-drug interactions between GWP42003-P/Placebo and CLB and between GWP42003 P/Placebo and N-CLB. A standard 90% confidence interval (CI) approach for the between time point ratios of geometric means of Cmax was carried out on a logarithmic scale using a linear mixed effect model. The no-effect boundary was set between 0.5 and 2.0, and if the 90% CI for the ratio of the geometric means of a PK variable fell within the interval [0.5, 2.0], a lack of meaningful effect was declared. Estimates were back transformed to provide summaries on the original scale. The model included a fixed effect term for PK assessment period. An unstructured covariance matrix was used. Kenward and Roger's method was used to calculate the denominator degrees of freedom for the fixed effects.

End point type	Primary

End point timeframe:

Predose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 12, and 24 h postdose on Days 1 and 33

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The Day 33 compared to Day 1 geometric mean ratios of CLB and N-CLB were calculated for Cmax, with a standard 90% CI.

End point values	Period 1: GWP42003-P	Period 1: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: Ratio				
number (confidence interval 90%)				
Geometric Mean Ratio of CLB, Cmax	0.997 (0.834 to 1.19)	1.05 (0.401 to 2.74)		
Geometric Mean Ratio of N-CLB, Cmax	2.22 (1.42 to 3.46)	1.17 (0.628 to 2.17)		

Statistical analyses

No statistical analyses for this end point

Primary: Period 1: PK: Geometric Mean Ratios Of CLB And N-CLB For AUCtau On Day 33 Compared With Day 1

End point title	Period 1: PK: Geometric Mean Ratios Of CLB And N-CLB For AUCtau On Day 33 Compared With Day 1[5]

End point description:

The Day 33 compared to Day 1 geometric mean ratios of CLB and N-CLB were calculated for AUCtau to look for evidence of drug-drug interactions between GWP42003-P/Placebo and CLB and between GWP42003 P/Placebo and N-CLB. A standard 90% confidence interval (CI) approach for the between time point ratios of geometric means of AUCtau was carried out on a logarithmic scale using a linear mixed effect model. The no-effect boundary was set between 0.5 and 2.0, and if the 90% CI for the ratio of the geometric means of a PK variable fell within the interval [0.5, 2.0], a lack of meaningful effect was declared. Estimates were back transformed to provide summaries on the original scale. The model included a fixed effect term for PK assessment period. An unstructured covariance matrix was used. Kenward and Roger's method was used to calculate the denominator degrees of freedom for the fixed effects.

End point type	Primary

End point timeframe:

Predose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 12, and 24 h postdose on Days 1 and 33

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The Day 33 compared to Day 1 geometric mean ratios of CLB and N-CLB were calculated for AUCtau, with a standard 90% CI.

End point values	Period 1: GWP42003-P	Period 1: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: Ratio				
number (confidence interval 90%)				
Geometric Mean Ratio of CLB, AUCtau	1.06 (0.898 to 1.24)	0.996 (0.652 to 1.52)		
Geometric Mean Ratio of N-CLB, AUCtau	2.64 (1.95 to 3.58)	1.00 (0.795 to 1.27)		

Statistical analyses

No statistical analyses for this end point

Primary: Period 2: Number Of Participants Who Experienced Severe OLE-Emergent Adverse Events

End point title	Period 2: Number Of Participants Who Experienced Severe OLE-Emergent Adverse Events[6]

End point description:

An OLE-emergent adverse event (AE) was defined as an AE with an onset date after the first dose of IMP in the OLE phase of the study. The number of participants who experienced 1 or more severe OLE-emergent AEs after the first dose of IMP in the OLE phase of the study up to the Safety follow-up visit (28 [± 3] days following the last dose of IMP) is presented.
A summary of serious and all other non-serious AEs regardless of causality is located in the Adverse Events section.

End point type	Primary

End point timeframe:

Postdose on Day 2 of Visit 4 up to Safety follow-up (28 [± 3] days following the last dose of IMP)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Safety data in the OLE phase were analysed descriptively.

End point values	Period 2: GWP42003-P			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Number of Participants				
Overall Number of Participants Analyzed	18			
Number Of Participants With Severe OLE-Emergent AE	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Period 1: Number Of Participants Who Experienced Severe Treatment Emergent Adverse Events (TEAEs)

End point title	Period 1: Number Of Participants Who Experienced Severe Treatment Emergent Adverse Events (TEAEs)

End point description:

A TEAE was defined as an AE with an onset date on or after the first dose of IMP. If an AE had a partial onset date and it was unclear from the partial date (or the stop date) whether the AE started prior to or following the first dose of IMP then the AE was considered a TEAE. The number of participants who experienced 1 or more severe TEAEs after screening up to Day 71 is presented here.
A summary of serious and all other non-serious AEs regardless of causality is located in the Reported Adverse Events module.

End point type	Secondary

End point timeframe:

Postdose on Day 2 up to Safety follow-up (Day 71)

End point values	Period 1: GWP42003-P	Period 1: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	4		
Units: participants	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Period 1:
Postdose on Baseline (Day 1) up to Day 71

Period 2:
Postdose on Day 2 of Visit 4 up to Safety follow-up (28 [± 3] days following the last dose of IMP)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Period 1: GWP42003-P 20 mg/kg/Day Dose

Reporting group description:

Participants received GWP42003-P 20 mg/kg/day orally, twice daily immediately after their CLB dose. Participants titrated GWP42003-P to 20 mg/kg/day over 10 days and remained at this dose for the 21-day treatment period. Participants who then did not enter the OLE or withdrew early had a 10-day taper (10% per day) period. Participants who transferred to the OLE (still blinded at that stage) tapered off their GWP42003-P treatment by reducing their maintenance dose by 10% per day and concomitantly titrating GWP42003-P for the OLE.

All participants (in the GWP42003-P and Placebo treatment groups) were on a stable dose of CLB at Baseline, administered either once or twice daily as per the physician's preferred CLB dosing regimen for each participant, and continued taking CLB, as an IMP, for the duration of this study.

Reporting group title	Period 1: Placebo

Reporting group description:

Participants received placebo (0 mg/mL GWP42003-P) orally, twice daily immediately after the participant's CLB dose. Participants titrated the placebo dose over 10 days, followed by a 21-day treatment period. Participants who then did not enter the OLE or withdrew early had a 10-day taper (10% per day) period. Participants who transferred to the OLE (still blinded at that stage) tapered off their placebo treatment by reducing their maintenance dose by 10% per day and concomitantly titrating GWP42003-P for the OLE.

All participants (in the GWP42003-P and Placebo treatment groups) were on a stable dose of CLB at Baseline, administered either once or twice daily as per the physician's preferred CLB dosing regimen for each participant, and continued taking CLB, as an IMP, for the duration of this study.

Reporting group title	Period 2: GWP42003-P 20 mg/kg/Day Dose

Reporting group description:

The number of participants who experienced OLE-emergent AEs after the first dose of IMP in the OLE phase of the study up to the Safety follow-up visit (28 [± 3] days following the last dose of IMP) is presented. The OLE population was the primary analysis set for all safety endpoints reported. Participants' expected seizure types were not routinely documented as AEs. However, any worsening, including change in the pattern or severity of seizures, was documented as an AE.

Serious adverse events	Period 1: GWP42003-P 20 mg/kg/Day Dose	Period 1: Placebo	Period 2: GWP42003-P 20 mg/kg/Day Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	2 / 18 (11.11%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	

Investigations			
Alanine aminotransferase abnormal			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase abnormal			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase abnormal			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure cluster			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Period 1: GWP42003-P 20 mg/kg/Day Dose	Period 1: Placebo	Period 2: GWP42003-P 20 mg/kg/Day Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 16 (75.00%)	2 / 4 (50.00%)	17 / 18 (94.44%)

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	1	0	3
Feeling cold			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Gait disturbance			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Peripheral swelling			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 16 (0.00%)	1 / 4 (25.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed[1]	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nervousness			

subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Tearfulness			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Irritability			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	3
Abnormal behaviour			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Affect lability			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hallucination, visual			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	3
Panic attack			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Investigations			
Liver function test abnormal			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Eosinophil count increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Haemoglobin decreased			

subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Platelet count decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
White blood cell count decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Toxicity to various agents			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	2 / 16 (12.50%)	0 / 4 (0.00%)	4 / 18 (22.22%)
occurrences (all)	3	0	6
Dysarthria			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Headache			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	4 / 18 (22.22%)
occurrences (all)	1	0	13
Hypersomnia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Lethargy			

subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Memory impairment			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Sedation			
subjects affected / exposed	2 / 16 (12.50%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Somnolence			
subjects affected / exposed	2 / 16 (12.50%)	0 / 4 (0.00%)	7 / 18 (38.89%)
occurrences (all)	2	0	9
Speech disorder			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Dizziness postural			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Seizure			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	6 / 16 (37.50%)	1 / 4 (25.00%)	8 / 18 (44.44%)
occurrences (all)	11	1	25
Dyspepsia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	3 / 16 (18.75%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Vomiting			
subjects affected / exposed	3 / 16 (18.75%)	0 / 4 (0.00%)	3 / 18 (16.67%)
occurrences (all)	5	0	4

Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	2 / 16 (12.50%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Petechiae			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Rash pruritic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	2
Pruritus			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Skin lesion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Back pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	3
Cystitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	3
Eczema infected			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Infected bite			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Tonsillitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hypovolaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 4 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The reporting group includes males. The AE of irregular menstruation can only affect females, and there are 8 total females exposed in the GWP42003-P group and 2 females exposed in the Placebo group in Period 1, and 8 females exposed in Period 2.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 July 2015	Study Design • The study design was changed from single-blind to double-blind and applicable visit days were revised. • The screening and maintenance periods were increased. Procedures • Procedures were revised to include serum alcohol tests and blood draws for CYP2C19 and 3A4 genetic testing and a Study Medication Use and Behavior Survey. Participant height measurement was removed. IMP • Information pertaining to the IMP, including color of IMP and guidance for IMP reduction, and IMP nomenclature, was added. CLB was designated as the IMP for the blinded phase of the study. • Secondary Endpoints • PK Parameters or THC and major metabolites as well as a safety assessment for drug abuse liability were added. Inclusion/Exclusion/Withdrawal Criteria • Revisions to inclusion criteria describing to seizure type, intervention with VNS, ketogenic diet, and alcohol consumption, contraception, pregnancy, and withdrawal if another IMP is taken were added. • Clarification of liver function testing related to drug-induced liver injury and eligibility criterion related to hepatic impairment were added.
08 October 2015	Secondary Endpoints • Analysis of the secondary blood draw samples for CYP2C19 and 3A4 genotype analysis added. Procedures • Clarification text added stating that participants must remain at the clinic for at least 30 minutes on Visit 2, Day 2 to monitor for adverse reactions. • Clarification text added stating that the evening dose of GWP42003-P/placebo and any AEDs must be taken 12 hours after the PK blood draw. • Clarification text added stating that the dose of GWP42003-P can only be adjusted to 30 mg/kg/day from Visit 5 onwards to allow participants to titrate up to 20 mg/kg/day prior to any further dose increases. Exclusion/Withdrawal Criteria • Exclusion criterion of participants taking felbamate for less than 1 year prior to screening added, to mitigate the risks associated with felbamate treatment, which are greatest within the first year of treatment. • Travel outside of the country of residence exclusion criterion amended to be allowed if the IMP was permitted in that country. • Exclusion criterion of participants with prolonged QTcB (> 450 msec for males and > 470 msec for females) added as safety precaution as the formal QT interval corrected for heart rate (QTc) study had not been completed. • Addition of the withdrawal criterion of participants with a significant change in QTcB (> 60 msec) from the previous ECG or absolute QTcB of > 500 msec as the formal QTc study had not been completed. Laboratory Tests • PK analysis for CBD, THC, and their major metabolites not to be conducted at Visit 2 as the participants would not be exposed at that time. • STP, VPA, LEV, and TPM PK analysis to be conducted at Visit 2 if the participants were taking them. • Addition of gamma-glutamyltransferase added to the list of liver enzymes to be analyzed at the request of the Food and Drug Administration. • Participants with elevated liver enzymes had to go back to the site for repeat testing.

04 February 2016	Inclusion Criteria • Upper age limit of the inclusion criteria was amended to 65 years to expand the trial to more participants. Procedures • Clarification text was added stating that participants had to remain at the clinic for at least 30 minutes if they were changing from placebo to GWP42003-P during the OLE period. • Clarification that during the OLE period, 1 month was equal to 28 days or 4 weeks.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported