Clinical trial results:
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

Summary

EudraCT number	2014-002940-42
Trial protocol	GB ES
Global end of trial date	19 May 2016

Results information

Result version number	v1 (current)
This version publication date	23 September 2018
First version publication date	23 September 2018

Trial information

Trial identification

Sponsor protocol code	GWEP1414

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02224560
WHO universal trial number (UTN)	-

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	GW Research Ltd., Alternate contact: medinfo@greenwichbiosciences.com, medinfo@gwpharm.com
Scientific contact	GW Research Ltd., Alternate contact: medinfo@greenwichbiosciences.com, medinfo@gwpharm.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001964-PIP01-16
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	19 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 May 2016
Global end of trial reached?	Yes
Global end of trial date	19 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was 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).

Protection of trial subjects:

This study was conducted in accordance with International Conference on 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 a study is conducted. No study procedures were performed on study candidates until written consent had been obtained from the participant's parent(s)/legal representative(s) and, if appropriate, written assent 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	08 June 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	United States: 181
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Spain: 32
Worldwide total number of subjects	225
EEA total number of subjects	44

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 months)	0
Children (2-11 years)	99
Adolescents (12-17 years)	59
Adults (18-64 years)	67
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The dose levels of 10 and 20 milligram (mg) per kilogram (kg) per day (mg/kg/day) were recommended by the Data Safety Monitoring Committee (DSMC) of study GWEP1332 Part A (NCT02091206) after assessment of safety and pharmacokinetic data. Participants of GWEP1414 were not enrolled until the DSMC had reviewed the safety data of GWEP1332 Part A.

Period 1

Period 1 title	Baseline, Treatment, and Follow-up (overall period)
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	GWP42003-P 20 mg/kg/day Dose

Arm description:

Participants received GWP42003-P 20 milligrams (mg) per kilogram (kg) per day (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 open label extension (OLE) study, the maintenance period was followed by a 10-day taper (10% per day) period.

Arm type	Experimental
Investigational medicinal product name	GWP42003-P
Investigational medicinal product code	
Other name	Cannabidiol, CBD, Epidiolex
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	GWP42003-P 10 mg/kg/day Dose

Arm description:

Participants received GWP42003-P 10 mg/kg/day administered orally, half in the morning and half in the evening. Participants titrated GWP42003-P to 10 mg/kg/day over 7 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.

Arm type	Experimental
Investigational medicinal product name	GWP42003-P
Investigational medicinal product code	
Other name	Cannabidiol, CBD, Epidiolex
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).

Arm title	Placebo

Arm description:

Participants received placebo (0 mg/mL CBD) volume matched to 1 of the 2 dose levels (10 or 20 mg/kg/day), 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 7 to 11 days according to the matched investigational medicinal product (IMP) group (7 or 11 days for the 10 or 20 mg/kg/day GWP42003-P groups, respectively) 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 of the matched dose) period.

Arm type	Placebo
Investigational medicinal product name	Placebo control
Investigational medicinal product code	
Other name	Placebo
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	GWP42003-P 20 mg/kg/day Dose	GWP42003-P 10 mg/kg/day Dose	Placebo
Started	76	73	76
Intent to Treat (ITT) Analysis Set	76	73	76
Completed	67	71	74
Not completed	9	2	2
Withdrawn by investigator	1	1	-
Met withdrawal criteria	1	-	-
Adverse event	4	1	1
Withdrawal by Subject	2	-	1
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Baseline, Treatment, and Follow-up

Reporting group description:

ITT Analysis Set: Received at least 1 dose of IMP with at least 1 post-baseline efficacy endpoint measurement. Participants were analyzed according to the treatment group to which they were randomized.

Reporting group values	Baseline, Treatment, and Follow-up	Total	
Number of subjects	225	225	
Age categorical Units: Subjects			
Children (2-11 years)	99	99	
Adolescents (12-17 years)	59	59	
Adults (18-64 years)	67	67	
Age continuous Units: years			
arithmetic mean	15.6		
standard deviation	± 9.8	-	
Gender categorical Units: Subjects			
Female	96	96	
Male	129	129	

Subject analysis sets	
Subject analysis set title	GWP42003-P 20 mg/kg/day Dose-ITT Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received at least 1 dose of IMP with at least 1 post-baseline efficacy endpoint measurement; analyzed according to the treatment group to which they were randomized (GWP42003-P 20 mg/kg/day).

Subject analysis set title	GWP42003-P 10 mg/kg/day-ITT Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received at least 1 dose of IMP with at least 1 post-baseline efficacy endpoint measurement; analyzed according to the treatment group to which they were randomized (GWP42003-P 10 mg/kg/day).

Subject analysis set title	Placebo-ITT Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received at least 1 dose of IMP with at least 1 post-baseline efficacy endpoint measurement; analyzed according to the treatment group to which they were randomized (Placebo).

Reporting group values	GWP42003-P 20 mg/kg/day Dose-ITT Analysis Set	GWP42003-P 10 mg/kg/day-ITT Analysis Set	Placebo-ITT Analysis Set
Number of subjects	76	73	76

Age categorical Units: Subjects			
Children (2-11 years)	34	32	33
Adolescents (12-17 years)	20	19	20
Adults (18-64 years)	22	22	23
Age continuous Units: years			
arithmetic mean	16.0	15.4	15.3
standard deviation	± 10.8	± 9.5	± 9.3
Gender categorical Units: Subjects			
Female	31	33	32
Male	45	40	44

End points

End points reporting groups

Reporting group title	GWP42003-P 20 mg/kg/day Dose

Reporting group description:

Participants received GWP42003-P 20 milligrams (mg) per kilogram (kg) per day (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 open label extension (OLE) study, the maintenance period was followed by a 10-day taper (10% per day) period.

Reporting group title	GWP42003-P 10 mg/kg/day Dose

Reporting group description:

Participants received GWP42003-P 10 mg/kg/day administered orally, half in the morning and half in the evening. Participants titrated GWP42003-P to 10 mg/kg/day over 7 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.

Reporting group title	Placebo

Reporting group description:

Participants received placebo (0 mg/mL CBD) volume matched to 1 of the 2 dose levels (10 or 20 mg/kg/day), 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 7 to 11 days according to the matched investigational medicinal product (IMP) group (7 or 11 days for the 10 or 20 mg/kg/day GWP42003-P groups, respectively) 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 of the matched dose) period.

Subject analysis set title	GWP42003-P 20 mg/kg/day Dose-ITT Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received at least 1 dose of IMP with at least 1 post-baseline efficacy endpoint measurement; analyzed according to the treatment group to which they were randomized (GWP42003-P 20 mg/kg/day).

Subject analysis set title	GWP42003-P 10 mg/kg/day-ITT Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received at least 1 dose of IMP with at least 1 post-baseline efficacy endpoint measurement; analyzed according to the treatment group to which they were randomized (GWP42003-P 10 mg/kg/day).

Subject analysis set title	Placebo-ITT Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received at least 1 dose of IMP with at least 1 post-baseline efficacy endpoint measurement; analyzed according to the treatment group to which they were randomized (Placebo).

Primary: Percentage Change From Baseline In Drop Seizure Frequency During The Treatment Period

End point title	Percentage Change From Baseline In Drop Seizure Frequency During The Treatment Period

End point description:

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) x 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) x 28. Baseline included all available data prior to Day 1 (28-day average). Negative percentages show an improvement from baseline.

End point type	Primary

End point timeframe:

Baseline to End of Treatment (EOT) (Day 99) or Early Termination (ET)

End point values	GWP42003-P 20 mg/kg/day Dose-ITT Analysis Set	GWP42003-P 10 mg/kg/day-ITT Analysis Set	Placebo-ITT Analysis Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	76	73	76	
Units: percentage change				
median (inter-quartile range (Q1-Q3))	-41.86 (-72.4 to -1.3)	-37.16 (-63.8 to -5.6)	-17.17 (-37.1 to 0.9)	

Statistical analyses

Statistical analysis title	Change From Baseline In Drop Seizures 20 mg/kg/day

Statistical analysis description:

The P-value was calculated by using the Wilcoxon rank-sum test; the point estimate and confidence intervals were calculated by using the Hodges–Lehmann approach.

Comparison groups	GWP42003-P 20 mg/kg/day Dose-ITT Analysis Set v Placebo-ITT Analysis Set
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0047
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	-21.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.79
upper limit	-6.67

Statistical analysis title	Change From Baseline In Drop Seizures 10 mg/kg/day

Statistical analysis description:

The P-value was calculated by using the Wilcoxon rank-sum test; the point estimate and confidence intervals were calculated by using the Hodges–Lehmann approach.

Comparison groups	GWP42003-P 10 mg/kg/day-ITT Analysis Set v Placebo-ITT Analysis Set
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	-19.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.24
upper limit	-7.69

Secondary: Number Of Participants With A ≥50% Reduction From Baseline In Drop Seizure Frequency During The Treatment Period

End point title	Number Of Participants With A ≥50% Reduction From Baseline In Drop Seizure Frequency During The Treatment Period

End point description:

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.

End point type	Secondary

End point timeframe:

Baseline to EOT (Day 99) or ET

End point values	GWP42003-P 20 mg/kg/day Dose-ITT Analysis Set	GWP42003-P 10 mg/kg/day-ITT Analysis Set	Placebo-ITT Analysis Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	76	73	76	
Units: participants	30	26	11	

Statistical analyses

Statistical analysis title	Number of 50% Responders 20 mg/kg/day
Comparison groups	GWP42003-P 20 mg/kg/day Dose-ITT Analysis Set v Placebo-ITT Analysis Set
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.75
upper limit	8.47

Notes:

[1] - Calculated using a Cochran-Mantel-Haenszel (CMH) test stratified by age group (2-5, 6-11, 12-17 and 18-55 years)

Statistical analysis title	Number of 50% Responders 10 mg/kg/day
Comparison groups	GWP42003-P 10 mg/kg/day-ITT Analysis Set v Placebo-ITT Analysis Set
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.47
upper limit	7.26

Notes:

[2] - Calculated using a CMH test stratified by age group (2-5, 6-11, 12-17 and 18-55 years)

Secondary: Percentage Change From Baseline In Total Seizure Frequency During The Treatment Period

End point title	Percentage Change From Baseline In Total Seizure Frequency During The Treatment Period

End point description:

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.

End point type	Secondary

End point timeframe:

Baseline to EOT (Day 99) or ET

End point values	GWP42003-P 20 mg/kg/day Dose-ITT Analysis Set	GWP42003-P 10 mg/kg/day-ITT Analysis Set	Placebo-ITT Analysis Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	76	73	76	
Units: percentage change				
median (inter-quartile range (Q1-Q3))	-38.40 (-64.6 to -0.7)	-36.44 (-64.5 to -10.8)	-18.47 (-39.0 to 0.5)	

Statistical analyses

Statistical analysis title	Change in Total Seizure Frequency 20 mg/kg/day

Statistical analysis description:

The P-value was calculated by using the Wilcoxon rank-sum test; the point estimate and confidence intervals were calculated by using the Hodges–Lehmann approach.

Comparison groups	GWP42003-P 20 mg/kg/day Dose-ITT Analysis Set v Placebo-ITT Analysis Set

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0091
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	-18.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.8
upper limit	-4.43

Statistical analysis title	Change in Total Seizure Frequency 10 mg/kg/day

Statistical analysis description:

The P-value was calculated by using the Wilcoxon rank-sum test; the point estimate and confidence intervals were calculated by using the Hodges–Lehmann approach.

Comparison groups	GWP42003-P 10 mg/kg/day-ITT Analysis Set v Placebo-ITT Analysis Set
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	-19.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.37
upper limit	-7.47

Secondary: Subject/Caregiver Global Impression Of Change (S/CGIC) Assessment

End point title	Subject/Caregiver Global Impression Of Change (S/CGIC) Assessment

End point description:

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.

End point type	Secondary

End point timeframe:

Baseline to Last Visit (Day 99) or ET

End point values	GWP42003-P 20 mg/kg/day Dose-ITT Analysis Set	GWP42003-P 10 mg/kg/day-ITT Analysis Set	Placebo-ITT Analysis Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	75	73	75	
Units: participants				
Very Much Improved	6	9	1	
Much Improved	15	14	8	
Slightly Improved	22	25	24	
No Change	25	21	35	
Slightly Worse	6	3	4	
Much Worse	1	1	3	
Very Much Worse	0	0	0	

Statistical analyses

Statistical analysis title	S/CGIC 20 mg/kg/day
Statistical analysis description:	
The OR represents the odds of participant recording a lower score (improvement) on a continuous scale.	
Comparison groups	GWP42003-P 20 mg/kg/day Dose-ITT Analysis Set v Placebo-ITT Analysis Set
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0439 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	3.3

Notes:

[3] - Ordinal logistic regression model with treatment group as a fixed factor.

Statistical analysis title	S/CGIC 10 mg/kg/day
Statistical analysis description:	
The OR represents the odds of participant recording a lower score (improvement) on a continuous scale.	
Comparison groups	GWP42003-P 10 mg/kg/day-ITT Analysis Set v Placebo-ITT Analysis Set

Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.41
upper limit	4.66

Notes:

[4] - Ordinal logistic regression model with treatment group as a fixed factor

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 through Day 137 (Safety Follow-up)

Adverse event reporting additional description:

Safety Analysis Set: Received at least 1 dose of IMP; analyzed as per actual treatment received. Six participants who were assigned to the GWP42003-P 10 mg/kg/day dose received dosing schedules for GWP42003-P 20 mg/kg/day. For safety analyses, these participants were assigned to the GWP42003-P 20 mg/kg/day group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	GWP42003-P 20 mg/kg/day Dose-Safety Analysis Set

Reporting group description:

Participants received at least 1 dose of IMP; analyzed as per actual treatment received. Six participants who were assigned to the GWP42003-P 10 mg/kg/day dose received dosing schedules for GWP42003-P 20 mg/kg/day. For safety analyses, these participants were assigned to the GWP42003-P 20 mg/kg/day group.

Reporting group title	GWP42003-P 10 mg/kg/day Dose-Safety Analysis Set

Reporting group description:

Participants received at least 1 dose of IMP; analyzed as per actual treatment received. Six participants who were assigned to the GWP42003-P 10 mg/kg/day dose received dosing schedules for GWP42003-P 20 mg/kg/day. For safety analyses, these participants were assigned to the GWP42003-P 20 mg/kg/day group.

Reporting group title	Placebo-Safety Analysis Set

Reporting group description:

Participants received at least 1 dose of IMP; analyzed as per actual treatment received.

Serious adverse events	GWP42003-P 20 mg/kg/day Dose-Safety Analysis Set	GWP42003-P 10 mg/kg/day Dose-Safety Analysis Set	Placebo-Safety Analysis Set
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 82 (15.85%)	13 / 67 (19.40%)	8 / 76 (10.53%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 82 (1.22%)	0 / 67 (0.00%)	0 / 76 (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
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 82 (1.22%)	1 / 67 (1.49%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 82 (1.22%)	0 / 67 (0.00%)	0 / 76 (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
Investigation			
subjects affected / exposed	0 / 82 (0.00%)	0 / 67 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 82 (0.00%)	1 / 67 (1.49%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Delayed recovery from anaesthesia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 67 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 82 (1.22%)	0 / 67 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	2 / 82 (2.44%)	0 / 67 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			

subjects affected / exposed	1 / 82 (1.22%)	0 / 67 (0.00%)	0 / 76 (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
Sedation			
subjects affected / exposed	0 / 82 (0.00%)	1 / 67 (1.49%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 82 (1.22%)	0 / 67 (0.00%)	0 / 76 (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
Status epilepticus			
subjects affected / exposed	4 / 82 (4.88%)	7 / 67 (10.45%)	3 / 76 (3.95%)
occurrences causally related to treatment / all	1 / 7	0 / 8	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 67 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Device malfunction			
subjects affected / exposed	1 / 82 (1.22%)	0 / 67 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 67 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 82 (1.22%)	0 / 67 (0.00%)	0 / 76 (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

Faecaloma			
subjects affected / exposed	0 / 82 (0.00%)	0 / 67 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 67 (1.49%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumatosis intestinalis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 67 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 82 (0.00%)	1 / 67 (1.49%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoventilation			
subjects affected / exposed	0 / 82 (0.00%)	1 / 67 (1.49%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 67 (1.49%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 82 (1.22%)	0 / 67 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 82 (0.00%)	1 / 67 (1.49%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 67 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 67 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 82 (2.44%)	3 / 67 (4.48%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 82 (0.00%)	1 / 67 (1.49%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 82 (1.22%)	0 / 67 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 82 (0.00%)	1 / 67 (1.49%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 67 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 67 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Upper respiratory tract infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 67 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 82 (0.00%)	1 / 67 (1.49%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
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	GWP42003-P 20 mg/kg/day Dose-Safety Analysis Set	GWP42003-P 10 mg/kg/day Dose-Safety Analysis Set	Placebo-Safety Analysis Set
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 82 (76.83%)	36 / 67 (53.73%)	40 / 76 (52.63%)
Nervous system disorders			
Convulsion			
subjects affected / exposed	5 / 82 (6.10%)	2 / 67 (2.99%)	7 / 76 (9.21%)
occurrences (all)	6	3	7
Headache			
subjects affected / exposed	5 / 82 (6.10%)	2 / 67 (2.99%)	3 / 76 (3.95%)
occurrences (all)	5	5	5
Lethargy			
subjects affected / exposed	5 / 82 (6.10%)	3 / 67 (4.48%)	2 / 76 (2.63%)
occurrences (all)	5	3	2
Somnolence			
subjects affected / exposed	25 / 82 (30.49%)	14 / 67 (20.90%)	4 / 76 (5.26%)
occurrences (all)	31	20	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 82 (9.76%)	5 / 67 (7.46%)	2 / 76 (2.63%)
occurrences (all)	11	5	2
Pyrexia			
subjects affected / exposed	9 / 82 (10.98%)	6 / 67 (8.96%)	12 / 76 (15.79%)
occurrences (all)	14	7	18

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 82 (14.63%)	7 / 67 (10.45%)	6 / 76 (7.89%)
occurrences (all)	16	7	9
Vomiting			
subjects affected / exposed	10 / 82 (12.20%)	4 / 67 (5.97%)	9 / 76 (11.84%)
occurrences (all)	19	5	10
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 82 (4.88%)	4 / 67 (5.97%)	2 / 76 (2.63%)
occurrences (all)	5	4	2
Irritability			
subjects affected / exposed	4 / 82 (4.88%)	6 / 67 (8.96%)	2 / 76 (2.63%)
occurrences (all)	4	6	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 82 (10.98%)	3 / 67 (4.48%)	5 / 76 (6.58%)
occurrences (all)	10	4	6
Upper respiratory tract infection			
subjects affected / exposed	10 / 82 (12.20%)	11 / 67 (16.42%)	11 / 76 (14.47%)
occurrences (all)	10	13	13
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 82 (25.61%)	11 / 67 (16.42%)	6 / 76 (7.89%)
occurrences (all)	23	13	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2015	This amendment addressed the following issues: * Clarified the definition of drop seizures. * Updated secondary objectives to include "Change in duration of subtypes of seizures". * Updated eligibility criteria for the electroencephalogram. * Clarified criteria for withdrawal. * Updated contact details in line with a change in GW Research Ltd's business address. * Changed the visit windows. * Included a review of seizure history by the Epilepsy Study Consortium. * Specified that participants would be stratified by age across treatment arms. * Amended wording to allow participants who suspended IMP due to an adverse event to resume dosing prior to complete recovery, provided that the adverse event was well tolerated. * Added recording of additional medical history including antiepileptic drugs (AEDs) and epilepsy-specific genetic testing. * Included additional questionnaires: Subject/Caregiver Global Impression of Change in Seizure Duration (S/CGICSD) and Pediatric Cannabinoid Withdrawal Scale. * Revised ITT analysis set criteria per Food and Drug Administration (FDA) request. * Modified statistical analysis testing of the primary endpoint and additional statistical analysis of the secondary endpoints. * Amended the exclusion criteria to include contraception requirements and previous cannabis use. * Changed the statistical methods dealing with missing data. * Clarified that IMP usage was to be recorded via the paper diary to reduce the IVRS call time. * Incorporated additional assessments: pharmacokinetic, Cognitive Assessment Battery (CAB), Growth and Development measurements, insulin-like growth factor-1 levels, menstruation, and Tanner Staging per FDA request. * Updated references to reflect the latest safety information. * Corrected minor spelling/formatting/consistency issues.

11 June 2015	This amendment incorporated recommendations received from the United States competent authority (FDA). * Added measurement of serum triglycerides. * Clarified that the EOT visit would also be labeled as the Withdrawal visit. * Added 12-lead electrocardiogram and clinical laboratory assessments at the 'End of Taper' visit for participants who withdrew early and tapered IMP and for participants who opted not to enter the OLE study. * Clarified that during the follow-up of participants with potential cases of drug-induced liver injury, the levels of alanine or aspartate aminotransferase, total bilirubin, and alkaline phosphatase should be monitored until levels normalized or returned to normal. * Updated statistical analysis of the primary and secondary endpoints to include the full treatment period. * Updated lower age limit for Tanner Staging to include participants aged 10–17 (inclusive) or earlier if clinically indicated. * Specified that participants would be stratified by 4 age groups (2–5, 6–11, 12–17, and 18–55 years). In addition, the following changes were addressed: * Replaced wording of concomitant AED blood sampling in the event of an adverse event. * Clarification that the growth and development endpoint will only be assessed in participants < 18 years old. * Reclassified effects on menstruation as a safety measure. * Increased the number of participants per treatment group from 40 to 50 and amended the assumption that participants in the placebo group would experience a mean reduction in drop seizure frequency of 10% to 18%. * Replaced "High Dose Level" and "Low Dose Level" with "20 mg/kg/day" and "10 mg/kg/day," respectively. * Clarified eligibility criteria. * Clarified blood sampling was only to be taken from participants weighing ≥ 20 kg. * Clarified statistical methods and liver function testing. * Removed the Socioeconomic Scale item from the CAB. * Amended responder and sensitivity analysis and the CGIC/CGICSD questionnaires.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29768152