



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	2014-002941-23
Trial protocol	NL PL
Global end of trial date	18 March 2016

Results information

Result version number	v1 (current)
This version publication date	27 September 2018
First version publication date	27 September 2018

Trial information

Trial identification

Sponsor protocol code	GWEP1423
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02224690
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, GW Research Ltd., medinfo@gwpharm.com
Scientific contact	GW Research Ltd., 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)	Yes
EMA paediatric investigation plan number(s)	EMA-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	24 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 March 2016
Global end of trial reached?	Yes
Global end of trial date	18 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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 Council on Harmonisation (ICH) 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 site.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 April 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	Netherlands: 5
Country: Number of subjects enrolled	Poland: 38
Country: Number of subjects enrolled	United States: 128
Worldwide total number of subjects	171
EEA total number of subjects	43

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)	76
Adolescents (12-17 years)	37
Adults (18-64 years)	58
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The dose level of 20 milligram per kilogram per day (mg/kg/day) was recommended by the Data Safety Monitoring Committee (DSMC) of study GWEP1332 Part A (NCT02091206) after assessment of safety/pharmacokinetic data. The investigational medicinal product (IMP) was given daily in 2 doses to align with the preferred regimen for anti-epileptic drugs.

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 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 liquid, 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	Placebo
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Arm description:

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.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
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	Placebo
Started	86	85
Intent to Treat (ITT) Analysis Set	86	85
Safety Analysis Set	86	85
Completed	72	84
Not completed	14	1
Use of G-tube	1	-
Adverse Event	8	1
Did not meet eligibility criteria	1	-
Met Withdrawal Criteria	4	-

Baseline characteristics

Reporting groups

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

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 open label extension (OLE) study, the maintenance period was followed by a 10-day taper (10% per day) period.

Reporting group title	Placebo
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Reporting group description:

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.

Reporting group values	GWP42003-P 20 mg/kg/day Dose	Placebo	Total
Number of subjects	86	85	171
Age categorical Units: Subjects			
2-11 years	37	39	76
12-17 years	19	18	37
18-64 years	30	28	58
Age continuous Units: years			
arithmetic mean	15.478	15.284	
standard deviation	± 8.685	± 9.7945	-
Gender categorical Units: Subjects			
Female	41	42	83
Male	45	43	88

End points

End points reporting groups

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

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 open label extension (OLE) study, the maintenance period was followed by a 10-day taper (10% per day) period.

Reporting group title	Placebo
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Reporting group description:

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.

Subject analysis set title	GWP42003-P 20 mg/kg/day Dose-ITT Set
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Subject analysis set type	Intention-to-treat
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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 received (GWP42003-P 20 mg/kg/day).

Subject analysis set title	Placebo-ITT Set
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Subject analysis set type	Intention-to-treat
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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 received (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
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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: $([\text{frequency during the treatment period} - \text{frequency during baseline}] / \text{frequency during baseline}) * 100$. The frequency during each period was based on 28-day averages and calculated as: $(\text{number of seizures in the period} / \text{number of reported days in the IVRS period}) * 28$. Baseline included all available data prior to Day 1 (28-day average). Negative percentages show an improvement from baseline.

End point type	Primary
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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 Set	Placebo-ITT Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	85		
Units: percentage change				
median (inter-quartile range (Q1-Q3))	-43.90 (-69.62 to 1.93)	-21.80 (-45.72 to 1.74)		

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 Set v Placebo-ITT Set
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0135
Method	Wilcoxon rank sum test
Parameter estimate	Mean difference (final values)
Point estimate	-17.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.32
upper limit	-4.09

Secondary: Participants With $\geq 50\%$ Reduction From Baseline in Drop Seizure Frequency During The Treatment Period

End point title	Participants With $\geq 50\%$ 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 Set	Placebo-ITT Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	86		
Units: Participants	38	20		

Statistical analyses

Statistical analysis title	Number Of 50% Responders 20 mg/kg/day
Comparison groups	GWP42003-P 20 mg/kg/day Dose-ITT Set v Placebo-ITT Set
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0043 ^[1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.33
upper limit	4.97

Notes:

[1] - Calculated using a Cochran-Mantel-Haenszel 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
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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
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End point timeframe:

Baseline to EOT (Day 99) or ET

End point values	GWP42003-P 20 mg/kg/day Dose-ITT Set	Placebo-ITT Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	85		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-41.24 (-62.85 to -13.00)	-13.70 (-45.00 to 7.27)		

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 Set v Placebo-ITT Set

Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	Wilcoxon rank sum test
Parameter estimate	Median difference (final values)
Point estimate	-21.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.26
upper limit	-9.37

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

End point title	Subject/Caregiver Global Impression Of Change (S/CGIC)
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 Set	Placebo-ITT Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	85		
Units: Participants				
Very Much Improved	15	5		
Much Improved	14	9		
Slightly Improved	20	15		
No Change	27	43		
Slightly Worse	7	9		
Much Worse	1	2		
Very Much Worse	0	2		

Statistical analyses

Statistical analysis title	Subject/Caregiver Global Impression Of Change
Statistical analysis description:	
The odds ratio represents the odds of participant recording a lower score (improvement) on a continuous scale.	
Comparison groups	GWP42003-P 20 mg/kg/day Dose-ITT Set v Placebo-ITT Set
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.0012
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.45
upper limit	4.47

Notes:

[2] - 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: All participants randomized to treatment who received at least 1 dose of IMP. Participants were analyzed according to the treatment group to which they received.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

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

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.

Reporting group title	Placebo- Safety Set
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Reporting group description:

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.

Serious adverse events	GWP42003-P 20 mg/kg/day Dose- Safety Set	Placebo- Safety Set	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 86 (23.26%)	4 / 85 (4.71%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 86 (4.65%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 86 (4.65%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug level increased			

subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 86 (3.49%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 86 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	2 / 86 (2.33%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 86 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lethargy			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure cluster			
subjects affected / exposed	1 / 86 (1.16%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 86 (1.16%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			

subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	3 / 86 (3.49%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial secretion retention			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 86 (2.33%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 86 (1.16%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			

subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 86 (3.49%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	2 / 86 (2.33%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia adenoviral			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			

subjects affected / exposed	0 / 86 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 86 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 86 (0.00%)	2 / 85 (2.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	GWP42003-P 20 mg/kg/day Dose-Safety Set	Placebo- Safety Set	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 86 (61.63%)	43 / 85 (50.59%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	12 / 86 (13.95%)	8 / 85 (9.41%)	
occurrences (all)	13	8	
Sedation			
subjects affected / exposed	7 / 86 (8.14%)	1 / 85 (1.18%)	
occurrences (all)	8	1	
Convulsion			
subjects affected / exposed	3 / 86 (3.49%)	5 / 85 (5.88%)	
occurrences (all)	3	5	
Headache			
subjects affected / exposed	2 / 86 (2.33%)	5 / 85 (5.88%)	
occurrences (all)	2	7	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	11 / 86 (12.79%)	7 / 85 (8.24%)	
occurrences (all)	14	8	
Fatigue			
subjects affected / exposed	5 / 86 (5.81%)	2 / 85 (2.35%)	
occurrences (all)	6	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	16 / 86 (18.60%)	7 / 85 (8.24%)	
occurrences (all)	18	8	
Vomiting			
subjects affected / exposed	8 / 86 (9.30%)	14 / 85 (16.47%)	
occurrences (all)	16	16	
Constipation			
subjects affected / exposed	5 / 86 (5.81%)	4 / 85 (4.71%)	
occurrences (all)	5	4	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	7 / 86 (8.14%)	2 / 85 (2.35%)	
occurrences (all)	7	2	
Cough			
subjects affected / exposed	5 / 86 (5.81%)	2 / 85 (2.35%)	
occurrences (all)	5	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	6 / 86 (6.98%)	1 / 85 (1.18%)	
occurrences (all)	7	1	
Infections and infestations			
Sinusitis			
subjects affected / exposed	5 / 86 (5.81%)	2 / 85 (2.35%)	
occurrences (all)	5	2	
Upper respiratory tract infection			
subjects affected / exposed	2 / 86 (2.33%)	6 / 85 (7.06%)	
occurrences (all)	2	6	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	11 / 86 (12.79%)	2 / 85 (2.35%)	
occurrences (all)	11	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2014	• Clarified the definition of drop seizure. • Added a secondary objective/endpoint to evaluate change in duration of subtypes of seizures as assessed by the Combined Subject/Caregiver Global Impression of Change Score. • Clarified the exclusion criteria addressing previous and current use of cannabinoids. • Added additional collection of a full record of epilepsy-specific genetic testing and prior antiepileptic drugs taken as part of the participant's medical history for safety assessment and to aid/confirm diagnosis of LGS. • Clarified that IMP usage was recorded via the paper diary in order to reduce the IVRS call time. • Clarified that the baseline period must be a minimum of 28 days in order to capture sufficient baseline data. • Clarified that the safety follow-up period must be a minimum of 28 days after EOT in order to capture sufficient safety data. • Clarified the subtypes of seizures and definition of "countable partial seizures" in order to aid identification of seizure types. • Clarified that the pre-randomization pregnancy test was performed using urine rather than serum in order to provide an immediate result for assessment of inclusion/exclusion criteria. • Added the Pediatric Cannabinoid Withdrawal Scale for children 4–17 years of age.
05 February 2015	• Clarified the definition of drop seizures by removal of 'clonic' and 'myoclonic' from the definition. • Clarified the criteria for withdrawal. • Added the following assessments to reflect the addition of secondary objectives: Pharmacokinetics, Cognitive Assessment Battery, Growth and Development measurements, Insulin-like growth factor-1 levels, menstruation and Tanner Staging. • Updated references to reflect the latest safety information.

03 June 2015	• Changed business address. • Added age ranges to participant growth and development monitoring of IGF-1 levels and Tanner Staging. • Reclassified menstruation as a safety measure, rather than an efficacy measure. • Clarified the PK monitoring of CBD and its major metabolites based on participants weight. • Clarified the statistical methods for the primary and secondary endpoints. • Clarified 'End of Treatment' visit and withdrawal visit procedures. • Clarified the exclusion criteria relating to hepatic function. • Added clinical laboratory sample measurement of serum triglycerides and blood urea nitrogen. • Added participant stratification by age across treatment arms. • Added follow-up procedures for potential cases of drug-induced liver injury. • Increased participant numbers based on expanded review of published clinical trial data. • Amended responder and sensitivity analysis. • Updated eligibility criteria contraception requirements. • Updated eligibility criteria compliance statement. • Updated the cognitive assessment battery by removing the Socioeconomic Scale test and allowing a +3 day window for completion on a separate day if necessary. • Added antiepileptic drug monitoring as secondary objective/endpoint. • Clarified liver function testing. • Updated recommended target dose and titration regimen based on the Data Safety Monitoring Committee of trial GWEP1332 Part A. • Clarified drop seizure inclusion criteria.
19 June 2015	• Clarification of eligibility was incorporated. • Clarification of trial procedures • Updated eligibility criteria regarding impaired hepatic function.

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/29395273>