Clinical trial results:
A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome.

Summary

EudraCT number	2014-002939-34
Trial protocol	GB ES NL PL
Global end of trial date	09 April 2018

Results information

Result version number	v1 (current)
This version publication date	11 August 2019
First version publication date	11 August 2019

Trial information

Trial identification

Sponsor protocol code	GWEP1424

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02224703
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, +44 1223 238170, medinfo@gwpharm.com
Scientific contact	GW Research Ltd., Alternate contact: medinfo@greenwichbiosciences.com, +44 1223 238170, 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	09 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 April 2018
Global end of trial reached?	Yes
Global end of trial date	09 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of GWP42003-P as an adjunctive antiepileptic treatment compared with placebo, with respect to the change during the treatment period of the study compared to baseline in convulsive seizure frequency. The dose response effect between 2 GWP42003-P dose levels and placebo was also explored. Convulsive seizures were defined as tonic-clonic, tonic, clonic, or atonic and nonconvulsive seizures as myoclonic, countable partial, other partial, or absence.

Protection of trial subjects:

This study was designed, conducted, recorded, and reported in accordance with ethical principles that have their origin in the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, and are consistent with International Council on Harmonisation Good Clinical Practice guidelines and in accordance with applicable local, federal, and regulatory agency regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 April 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 25
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Spain: 39
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	United States: 94
Worldwide total number of subjects	199
EEA total number of subjects	89

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	137
Adolescents (12-17 years)	59
Adults (18-64 years)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 43 sites screened participants and 38 sites (23 in the United States, 7 in Spain, 3 in Poland, 2 in Australia, 1 in Israel, and 2 in the Netherlands) randomized participants into the trial. Two sites selected (1 in Israel and 1 in the United States) did not screen any participants.

Pre-assignment

Screening details:

To assess eligibility, participants 2–18 years of age with Dravet syndrome had to be taking 1 or more antiepileptic drugs (AEDs) at a dose that had been stable for at least 4 weeks were screened. A total of 285 participants were screened, of which 199 were randomized.

Period 1

Period 1 title	Double-Blind Period (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	10 mg/kg/Day GWP42003-P

Arm description:

GWP42003-P oral solution (100 milligrams/milliliter [mg/mL] cannabidiol in sesame oil with anhydrous ethanol with added sweetener [sucralose] and strawberry flavoring). The 10 mg/kilogram (kg)/day dose was defined as 50% of the 20 mg/kg/day dose.

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

Dosage and administration details:

GWP42003-P was taken orally twice daily as directed by the investigator. Participants titrated GWP42003-P to 10 mg/kg/day over 7 days and remained at the target dose for the treatment period.

Arm title	20 mg/kg/Day GWP42003-P

Arm description:

GWP42003-P oral solution (100 mg/mL cannabidiol in sesame oil with anhydrous ethanol with added sweetener [sucralose] and strawberry flavoring). The 20 mg/kg/day dose was recommended by the Data Safety Monitoring Committee (DSMC) after assessment of safety and pharmacokinetic data from Part A of study GWEP1332 (2014-000995-24).

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

Dosage and administration details:

GWP42003-P was taken orally twice daily as directed by the investigator. Participants titrated GWP42003-P to 20 mg/kg/day over 11 days and remained at the target dose for the treatment period.

Arm title	Placebo Control

Arm description:

Excipients only. Participants were pooled from 2 placebo cohorts, half receiving 10 mg/kg/day dose-volume equivalent and half receiving 20 mg/kg/day dose-volume equivalent.

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

Dosage and administration details:

Placebo was taken orally twice daily as directed by the investigator.

Number of subjects in period 1	10 mg/kg/Day GWP42003-P	20 mg/kg/Day GWP42003-P	Placebo Control
Started	67	67	65
Received at Least 1 Dose of Study Drug	66	67	65
Intent to Treat (ITT) Analysis Set	66	67	65
Completed	64	61	65
Not completed	3	6	0
Withdrawn by investigator	1	-	-
Adverse event, non-fatal	-	5	-
Advised by medical monitor	1	-	-
Consent withdrawn by parent or guardian	-	1	-
Lack of efficacy	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	10 mg/kg/Day GWP42003-P
Reporting group description:	
GWP42003-P oral solution (100 milligrams/milliliter [mg/mL] cannabidiol in sesame oil with anhydrous ethanol with added sweetener [sucralose] and strawberry flavoring). The 10 mg/kilogram (kg)/day dose was defined as 50% of the 20 mg/kg/day dose.	
Reporting group title	20 mg/kg/Day GWP42003-P
Reporting group description:	
GWP42003-P oral solution (100 mg/mL cannabidiol in sesame oil with anhydrous ethanol with added sweetener [sucralose] and strawberry flavoring). The 20 mg/kg/day dose was recommended by the Data Safety Monitoring Committee (DSMC) after assessment of safety and pharmacokinetic data from Part A of study GWEP1332 (2014-000995-24).	
Reporting group title	Placebo Control
Reporting group description:	
Excipients only. Participants were pooled from 2 placebo cohorts, half receiving 10 mg/kg/day dose-volume equivalent and half receiving 20 mg/kg/day dose-volume equivalent.	

Reporting group values	10 mg/kg/Day GWP42003-P	20 mg/kg/Day GWP42003-P	Placebo Control
Number of subjects	67	67	65
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	47	47	43
Adolescents (12-17 years)	20	18	21
Adults (18-64 years)	0	2	1
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	9.208	9.263	9.617
standard deviation	± 4.2479	± 4.3060	± 4.5757
Gender categorical Units: Subjects			
Female	40	31	34
Male	27	36	31
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	0	1	4
Black or African American	1	0	4
White	58	64	55
Other	8	2	1

Reporting group values	Total		

Number of subjects	199		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	137		
Adolescents (12-17 years)	59		
Adults (18-64 years)	3		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	105		
Male	94		
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	1		
Asian	5		
Black or African American	5		
White	177		
Other	11		

End points

End points reporting groups

Reporting group title	10 mg/kg/Day GWP42003-P

Reporting group description:

GWP42003-P oral solution (100 milligrams/milliliter [mg/mL] cannabidiol in sesame oil with anhydrous ethanol with added sweetener [sucralose] and strawberry flavoring). The 10 mg/kilogram (kg)/day dose was defined as 50% of the 20 mg/kg/day dose.

Reporting group title	20 mg/kg/Day GWP42003-P

Reporting group description:

GWP42003-P oral solution (100 mg/mL cannabidiol in sesame oil with anhydrous ethanol with added sweetener [sucralose] and strawberry flavoring). The 20 mg/kg/day dose was recommended by the Data Safety Monitoring Committee (DSMC) after assessment of safety and pharmacokinetic data from Part A of study GWEP1332 (2014-000995-24).

Reporting group title	Placebo Control

Reporting group description:

Excipients only. Participants were pooled from 2 placebo cohorts, half receiving 10 mg/kg/day dose-volume equivalent and half receiving 20 mg/kg/day dose-volume equivalent.

Primary: Change In Convulsive Seizures During The Treatment Period Compared To Baseline

End point title	Change In Convulsive Seizures During The Treatment Period Compared To Baseline

End point description:

Convulsive seizures were defined as tonic–clonic, tonic, clonic, or atonic. Participants or their caregivers recorded the number and type of convulsive seizures each day from screening until completion of dosing using an interactive voice response system (IVRS) diary. The primary end point was analyzed using negative binomial regression on the sum of the convulsive seizure counts during the treatment period, based on the ITT analysis set. Baseline included all available data prior to Day 1. Data reported as the ratio of geometric least squares mean in convulsive seizures and expressed as a percentage reduction.

End point type	Primary

End point timeframe:

Baseline to Day 99 or Early Termination (ET)

End point values	10 mg/kg/Day GWP42003-P	20 mg/kg/Day GWP42003-P	Placebo Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66	67	65	
Units: Percentage reduction				
number (confidence interval 95%)	48.7 (37.9 to 57.6)	45.7 (34.2 to 55.2)	26.9 (11.9 to 39.4)	

Statistical analyses

Statistical analysis title	20 mg/kg/Day GWP42003-P, Placebo Control

Statistical analysis description:

Model includes total number of seizures as a response variable and age group, time (baseline and treatment period), treatment, and treatment by time interaction as fixed effects, and participant as a

random effect. Log-transformed number of days in which seizures were reported by period is included as an offset. Null hypothesis was that the ratio of GWP42003-P to placebo would be 1.

Comparison groups	20 mg/kg/Day GWP42003-P v Placebo Control
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0299
Method	Negative binomial regression
Parameter estimate	Treatment Ratio
Point estimate	0.743
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.568
upper limit	0.971

Statistical analysis title	10 mg/kg/Day GWP42003-P, Placebo Control

Statistical analysis description:

Model includes total number of seizures as a response variable and age group, time (baseline and treatment period), treatment, and treatment by time interaction as fixed effects, and participant as a random effect. Log-transformed number of days in which seizures were reported by period is included as an offset. Null hypothesis was that the ratio of GWP42003-P to placebo would be 1.

Comparison groups	10 mg/kg/Day GWP42003-P v Placebo Control
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0095
Method	Negative binomial regression
Parameter estimate	Treatment Ratio
Point estimate	0.702
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.538
upper limit	0.916

Secondary: Change In Total Seizures During The Treatment Period Compared To Baseline

End point title	Change In Total Seizures During The Treatment Period Compared To Baseline

End point description:

Total seizures were defined as the combination of convulsive and non-convulsive seizures. Convulsive seizures were defined as tonic–clonic, tonic, clonic, or atonic seizures. Non-convulsive seizures were defined as myoclonic, countable partial, other partial, or absence seizures. Participants or their caregivers recorded the number and type of convulsive seizures and non-convulsive seizures each day from screening until completion of dosing using an IVRS diary. Change compared to baseline was calculated as per the primary outcome measure. Data reported as the ratio of geometric least squares mean in total seizures and expressed as a percentage reduction.

End point type	Secondary

End point timeframe:

Baseline to Day 99 or ET

End point values	10 mg/kg/Day GWP42003-P	20 mg/kg/Day GWP42003-P	Placebo Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66	67	65	
Units: Percentage reduction				
number (confidence interval 95%)	56.4 (47.8 to 63.6)	47.3 (36.9 to 56.0)	29.7 (16.0 to 41.1)	

Statistical analyses

Statistical analysis title	20 mg/kg/Day GWP42003-P, Placebo Control

Statistical analysis description:

Model includes total number of seizures as a response variable and age group, time (baseline and treatment period), treatment, and treatment by time interaction as fixed effects, and participant as a random effect. Log-transformed number of days in which seizures were reported by period is included as an offset.

Comparison groups	Placebo Control v 20 mg/kg/Day GWP42003-P
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0255
Method	Negative binomial regression
Parameter estimate	Treatment Ratio
Point estimate	0.749
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.581
upper limit	0.965

Statistical analysis title	10 mg/kg/Day GWP42003-P, Placebo Control

Statistical analysis description:

Model includes total number of seizures as a response variable and age group, time (baseline and treatment period), treatment, and treatment by time interaction as fixed effects, and participant as a random effect. Log-transformed number of days in which seizures were reported by period is included as an offset.

Comparison groups	10 mg/kg/Day GWP42003-P v Placebo Control

Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Negative binomial regression
Parameter estimate	Treatment Ratio
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.481
upper limit	0.799

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

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

End point description:

Convulsive seizures were defined as tonic–clonic, tonic, clonic, or atonic. Participants or their caregivers recorded the number and type of convulsive seizures each day from screening until completion of dosing using an IVRS diary. Baseline included all available data prior to Day 1 (28-day average). 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).

End point type	Secondary

End point timeframe:

Baseline to Day 99 or ET

End point values	10 mg/kg/Day GWP42003-P	20 mg/kg/Day GWP42003-P	Placebo Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66[1]	67[2]	65[3]	
Units: Participants	29	33	17	

Notes:

[1] - ITT

[2] - ITT

[3] - ITT

Statistical analyses

Statistical analysis title	20 mg/kg/Day GWP42003-P, Placebo Control
Comparison groups	20 mg/kg/Day GWP42003-P v Placebo Control

Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0069 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.32
upper limit	5.7

Notes:

[4] - P-value calculated from a Cochran–Mantel–Haenszel test stratified by age group (2–5, 6–12, and 13–18 years).

Statistical analysis title	10 mg/kg/Day GWP42003-P, Placebo Control
Comparison groups	10 mg/kg/Day GWP42003-P v Placebo Control
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0332 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	4.62

Notes:

[5] - P-value calculated from a Cochran–Mantel–Haenszel test stratified by age group (2–5, 6–12, and 13–18 years).

Secondary: Caregiver Global Impression Of Change (CGIC) At The Last Visit

End point title	Caregiver Global Impression Of Change (CGIC) At The Last Visit

End point description:

On Day 1 (prior to receiving study drug), the caregiver was asked to write a brief description of the participant's overall condition as a memory aid for the CGIC questionnaire at subsequent visits. The CGIC questionnaire comprised the following question, to be rated on a 7-point scale: Since your child started treatment, please assess the status of your child's overall condition (comparing their condition now to their condition before treatment) using the scale below. The markers were: "Very Much Improved"; "Much Improved"; "Slightly Improved"; "No Change"; "Slightly Worse"; "Much Worse"; "Very Much Worse". The CGIC response/score, recorded at each visit, was summarized, on both a categorical and continuous scale, by treatment group. The scores at the last scheduled visit (not including the end of taper or safety follow-up visits) at which participant's last evaluation was performed were analyzed using ordinal logistic regression.

End point type	Secondary

End point timeframe:

Baseline to Last Visit

End point values	10 mg/kg/Day GWP42003-P	20 mg/kg/Day GWP42003-P	Placebo Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66[6]	66[7]	65[8]	
Units: Participants				
Very Much Improved	13	11	1	
Much Improved	11	10	8	
Slightly Improved	21	19	18	
No Change	18	17	32	
Slightly Worse	2	5	4	
Much Worse	1	3	2	
Very Much Worse	0	1	0	

Notes:

[6] - ITT

[7] - ITT

[8] - ITT

Statistical analyses

Statistical analysis title	20 mg/kg/Day GWP42003-P, Placebo Control
Comparison groups	Placebo Control v 20 mg/kg/Day GWP42003-P
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0279
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	3.78

Notes:

[9] - Proportional odds modelling was carried out by including treatment group as a fixed factor. The estimated OR tested the null hypothesis that OR was equal to 1.

Statistical analysis title	10 mg/kg/Day GWP42003-P, Placebo Control
Comparison groups	10 mg/kg/Day GWP42003-P v Placebo Control
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.0009
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.56
upper limit	5.53

Notes:

[10] - Proportional odds modelling was carried out by including treatment group as a fixed factor. The estimated OR tested the null hypothesis that OR was equal to 1.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 to Day 137.

Adverse event reporting additional description:

Safety Analysis Set: Received at least 1 dose of study drug and were analyzed per treatment received. Two participants randomized to receive GWP42003-P 10 mg/kg/day titrated above the target dose and were therefore assigned to the GWP42003-P 20 mg/kg/day group for all safety analyses.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	10 mg/kg/Day GWP42003-P

Reporting group description:

GWP42003-P oral solution (100 mg/mL cannabidiol in sesame oil with anhydrous ethanol with added sweetener [sucralose] and strawberry flavoring). The 10 mg/kg/day dose was defined as 50% of the 20 mg/kg/day dose.

Reporting group title	20 mg/kg/Day GWP42003-P

Reporting group description:

GWP42003-P oral solution (100 mg/mL cannabidiol in sesame oil with anhydrous ethanol with added sweetener [sucralose] and strawberry flavoring). The 20 mg/kg/day dose was recommended by the DSMC after assessment of safety and pharmacokinetic data from Part A of study GWEP1332 (2014-000995-24).

Reporting group title	Placebo Control

Reporting group description:

Excipients only. Participants were pooled from 2 placebo cohorts, half receiving 10 mg/kg/day dose-volume equivalent and half receiving 20 mg/kg/day dose-volume equivalent.

Serious adverse events	10 mg/kg/Day GWP42003-P	20 mg/kg/Day GWP42003-P	Placebo Control
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 64 (20.31%)	17 / 69 (24.64%)	10 / 65 (15.38%)
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	0 / 64 (0.00%)	1 / 69 (1.45%)	0 / 65 (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
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 64 (0.00%)	1 / 69 (1.45%)	0 / 65 (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
Liver function test abnormal			
subjects affected / exposed	0 / 64 (0.00%)	1 / 69 (1.45%)	0 / 65 (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
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	1 / 64 (1.56%)	1 / 69 (1.45%)	0 / 65 (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
Nervous system disorders			
Status epilepticus			
subjects affected / exposed	5 / 64 (7.81%)	7 / 69 (10.14%)	8 / 65 (12.31%)
occurrences causally related to treatment / all	0 / 5	0 / 12	0 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalized tonic-clonic seizure			
subjects affected / exposed	0 / 64 (0.00%)	1 / 69 (1.45%)	0 / 65 (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
Convulsion			
subjects affected / exposed	3 / 64 (4.69%)	0 / 69 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	2 / 64 (3.13%)	0 / 69 (0.00%)	0 / 65 (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
Seizure cluster			
subjects affected / exposed	1 / 64 (1.56%)	0 / 69 (0.00%)	2 / 65 (3.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Unresponsive to stimuli			
subjects affected / exposed	1 / 64 (1.56%)	0 / 69 (0.00%)	0 / 65 (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			
Pyrexia			
subjects affected / exposed	1 / 64 (1.56%)	1 / 69 (1.45%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug interaction			
subjects affected / exposed	0 / 64 (0.00%)	1 / 69 (1.45%)	0 / 65 (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
Fatigue			
subjects affected / exposed	0 / 64 (0.00%)	1 / 69 (1.45%)	0 / 65 (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
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 64 (0.00%)	1 / 69 (1.45%)	0 / 65 (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, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	1 / 64 (1.56%)	2 / 69 (2.90%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory depression			
subjects affected / exposed	0 / 64 (0.00%)	1 / 69 (1.45%)	0 / 65 (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 distress			

subjects affected / exposed	0 / 64 (0.00%)	0 / 69 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 64 (0.00%)	1 / 69 (1.45%)	0 / 65 (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
Psychiatric disorders			
Psychogenic seizure			
subjects affected / exposed	1 / 64 (1.56%)	0 / 69 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 64 (4.69%)	2 / 69 (2.90%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 64 (1.56%)	1 / 69 (1.45%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coxsackie viral infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 69 (1.45%)	0 / 65 (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
Gastroenteritis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 69 (1.45%)	0 / 65 (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
Sepsis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 69 (1.45%)	0 / 65 (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

Adenovirus infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 69 (0.00%)	0 / 65 (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
Laryngitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 69 (0.00%)	0 / 65 (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
Respiratory tract infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 69 (0.00%)	0 / 65 (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
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 64 (0.00%)	0 / 69 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 64 (1.56%)	1 / 69 (1.45%)	0 / 65 (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

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

Non-serious adverse events	10 mg/kg/Day GWP42003-P	20 mg/kg/Day GWP42003-P	Placebo Control
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 64 (87.50%)	60 / 69 (86.96%)	58 / 65 (89.23%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 64 (4.69%)	8 / 69 (11.59%)	0 / 65 (0.00%)
occurrences (all)	3	9	0
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 64 (4.69%)	8 / 69 (11.59%)	0 / 65 (0.00%)
occurrences (all)	3	9	0

Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 64 (6.25%)	4 / 69 (5.80%)	3 / 65 (4.62%)
occurrences (all)	4	4	3
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	1 / 64 (1.56%)	4 / 69 (5.80%)	0 / 65 (0.00%)
occurrences (all)	1	4	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	14 / 64 (21.88%)	16 / 69 (23.19%)	9 / 65 (13.85%)
occurrences (all)	17	20	9
Convulsion			
subjects affected / exposed	3 / 64 (4.69%)	4 / 69 (5.80%)	4 / 65 (6.15%)
occurrences (all)	3	6	5
Tremor			
subjects affected / exposed	0 / 64 (0.00%)	4 / 69 (5.80%)	0 / 65 (0.00%)
occurrences (all)	0	4	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	15 / 64 (23.44%)	14 / 69 (20.29%)	11 / 65 (16.92%)
occurrences (all)	21	22	15
Fatigue			
subjects affected / exposed	5 / 64 (7.81%)	14 / 69 (20.29%)	7 / 65 (10.77%)
occurrences (all)	7	17	8
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 64 (17.19%)	18 / 69 (26.09%)	8 / 65 (12.31%)
occurrences (all)	16	23	9
Vomiting			
subjects affected / exposed	4 / 64 (6.25%)	11 / 69 (15.94%)	4 / 65 (6.15%)
occurrences (all)	4	13	4
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	0 / 64 (0.00%)	1 / 69 (1.45%)	4 / 65 (6.15%)
occurrences (all)	0	1	4
Psychiatric disorders			

Aggression			
subjects affected / exposed	1 / 64 (1.56%)	6 / 69 (8.70%)	2 / 65 (3.08%)
occurrences (all)	1	6	2
Irritability			
subjects affected / exposed	3 / 64 (4.69%)	5 / 69 (7.25%)	2 / 65 (3.08%)
occurrences (all)	4	5	3
Abnormal behaviour			
subjects affected / exposed	0 / 64 (0.00%)	4 / 69 (5.80%)	0 / 65 (0.00%)
occurrences (all)	0	5	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 64 (6.25%)	8 / 69 (11.59%)	5 / 65 (7.69%)
occurrences (all)	4	11	6
Upper respiratory tract infection			
subjects affected / exposed	3 / 64 (4.69%)	4 / 69 (5.80%)	3 / 65 (4.62%)
occurrences (all)	3	4	3
Urinary tract infection			
subjects affected / exposed	0 / 64 (0.00%)	4 / 69 (5.80%)	1 / 65 (1.54%)
occurrences (all)	0	5	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	10 / 64 (15.63%)	19 / 69 (27.54%)	11 / 65 (16.92%)
occurrences (all)	10	19	13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2014	Addition of a secondary objective/end point to evaluate change in duration of subtypes of seizures as assessed by the Caregiver Global Impression of Change in Seizure Duration. Clarification of the exclusion criteria addressing previous and current use of cannabinoids. Additional collection of a full record of genetic testing and prior antiepileptic drugs taken as part of the participant's medical history for safety assessment and to aid/confirm diagnosis of Dravet Syndrome. Clarification that the baseline period must be a minimum of 28 days in order to capture sufficient baseline data. Clarification that the safety follow-up period must be a minimum of 28 days after end of treatment in order to capture sufficient safety data. Clarification of subtypes of seizures and definition of "countable partial seizures" in order to aid identification of seizure types. Clarification that the cognitive assessment battery will only be performed at sites that have the expertise to conduct the test. Pre-randomization pregnancy test to be performed using urine rather than serum in order to provide an immediate result for assessment of inclusion/exclusion criteria. Inclusion of the Pediatric Cannabinoid Withdrawal Scale for children 4–17 years of age.
20 November 2014	Cases of Drug-Induced Liver Injury must be a criterion for withdrawal from study treatment.

20 March 2015	Specified participants be stratified by age across treatment arms. Added assessment of growth and development through measurement of height, body weight, serum insulin-like growth factor 1 levels, and Tanner staging. Added measurement of effects of menstruation. Amended statistical methods for analysis of primary and secondary end points. Added blood sampling for pharmacokinetics (PK) analyses of cannabidiol and major metabolites. Added measurement of serum triglycerides in clinical laboratory assessments. Added electrocardiogram and clinical laboratory assessments at the 'End of Taper' visit for participants who withdrew early and tapered the investigational medicinal product (IMP) and for participants who opted not to enter the open-label extension. Increased the number of participants per treatment group from 40 to 50 (total increase from 120 to 150) and amended assumption that participants in the placebo group would experience a mean reduction in convulsive seizure frequency of 10 to 18%. Added eligibility criterion excluding participants taking felbamate for <1 year. Felbamate was also listed as a prohibited therapy if taken for <1 year. Clarified use of the Epilepsy study consortium to verify each participant's seizure subtypes and diagnosis of Dravet syndrome. Amended wording to allow participants who suspended IMP dosing due to an adverse event to resume dosing prior to complete recovery, provided that the adverse event was well tolerated. Added secondary end points to align the protocol with the open-label extension and edited primary and secondary end points to clarify that total number of convulsive and non-convulsive seizures would be measured. Clarified when the Cognitive Assessment Battery should be administered. Clarified that even though participants may achieve target dose before the end of the 2-week titration period, the titration period was 2 weeks to ensure all participants achieved stable dosing.

29 June 2015	Updated statistical analyses of the primary and secondary end points to include the full treatment period (titration plus maintenance period). Updated the lower age limit for Tanner Staging to include adolescent participants aged 10–17 (inclusive) or earlier if clinically indicated by the onset of menarche or other signs of precocious puberty. Replaced wording of concomitant AED blood sampling in the event of an adverse event with a secondary objective/end point requesting the investigator monitor plasma concomitant AED levels and discuss results with the GW medical monitor. Samples were only to be taken if the risk/benefit outcome was favorable, in the investigator's opinion. Reclassified effects on menstruation as a safety measure. Amended responder and sensitivity analyses to state the average number of seizures per 28 days rather than per week. Clarified the convulsive seizure inclusion criterion to state that only the first 28 days of the baseline period counted towards a participant's eligibility. Removed the Socioeconomic Scale test item (parent measure) from the Cognitive Assessment Battery as it was not possible to standardize this end point across different countries. Clarified blood sampling for PK was only to be taken from participants weighing ≥20 kg. Sampling times and windows were also clarified. Clarified the age restriction for Columbia-Suicide Severity Rating Scale suitability to include consideration of developmental delays as well as age.
23 February 2017	Increased the number of participants per treatment group from 50 to 62 (a total increase from 150 to 186). Changed the statistical analyses of seizure data to use nonparametric rather than parametric methods. Added assessments of plasma and urine concentrations of tetrahydrocannabinol and its major metabolites, and urine concentrations of cannabidiol and its major metabolites. Amended the PK parameters to allow for accurate determination of the defined parameters. Clarified that any clinical symptoms of concern resulting from possible drug-drug interactions should be discussed with the GW medical monitor and if required, adjustments to AEDs would be permitted. Broadened the mode of IMP administration to encompass participants who have difficulty swallowing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported