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

Summary

EudraCT number	2014-000995-24
Trial protocol	GB PL
Global end of trial date	26 November 2015

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	GWEP1332

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02091206
WHO universal trial number (UTN)	-
Other trial identifiers	NCT02091206: NCT number for GWEP1332A, NCT02091375: NCT Number for GWEP1332B

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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	26 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2015
Global end of trial reached?	Yes
Global end of trial date	26 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part A:
To evaluate the safety of multiple doses of GWP42003-P compared with placebo with respect to:
• Incidence, type and severity of adverse events (AEs).
• Effect on vital signs, physical examination parameters including weight.
• Effect on 12-lead electrocardiogram (ECG) findings.
• Effect on laboratory parameters.
• Changes in seizure frequency.
Part B:
• To assess the efficacy of GWP42003-P as an adjunctive antiepileptic treatment compared with placebo, with respect to the percentage change from baseline during the treatment period of the study in convulsive seizure frequency.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 October 2014
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 States: 102
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	France: 18
Worldwide total number of subjects	154
EEA total number of subjects	52

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)	110
Adolescents (12-17 years)	41
Adults (18-64 years)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This multi-center study consisted of 2 parts: Part A was a randomized, double-blind 21-day treatment study period. Part B was a randomized, double-blind, placebo-controlled, 14-week treatment study period that enrolled an entirely new group of participants, and those who failed the entry criteria for Part A were eligible to take part in Part B.

Period 1

Period 1 title	Parts A and B Combined (BL + treatment) (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	Part A GWP42003-P 5 mg/kg/day Dose

Arm description:

Participants received GWP42003-P 5 milligrams per kilogram per day (mg/kg/day) administered orally, half in the morning and half in the evening. Participants titrated GWP42003-P to 5 mg/kg/day over 3 days and remained at this dose for the rest of the 21-day treatment period (19 days). The 21-day treatment 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	Cannibidiol, CBD, Epidiolex
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

GWP42003-P was presented an oral solution containing 25 or 100 mg/milliliter (mL) cannabidiol (CBD) dissolved 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	Part A 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 rest of the 21-day treatment period (15 days). The 21-day treatment 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	Cannibidiol, CBD, Epidiolex
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

GWP42003-P was presented an oral solution containing 25 or 100 mg/mL CBD dissolved 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	Part A GWP42003-P 20 mg/kg/day Dose

Arm description:

Part A 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 rest of the 21-day treatment period (11 days). The 21-day treatment 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	Cannibidiol, CBD, Epidiolex
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

GWP42003-P was presented an oral solution containing 25 or 100 mg/mL CBD dissolved 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	Part A Placebo

Arm description:

Participants received placebo (0 mg/mL CBD), volume-matched to one of the 3 dose levels (5, 10, or 20 mg/kg/day), administered orally, half in the morning and half in the evening for 21 days. To maintain the blinded aspect of the study, participants titrated the placebo dose over 3 to 11 days according to the matched investigational medicinal product (IMP) group (3, 7, and 11 days for the 5, 10, or 20 mg/kg/day GWP42003-P groups, respectively) and remained at this dose for the rest of the 21-day treatment period. The 21-day treatment period was followed by a 10-day taper (10% per day of the matched dose) period.

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

Dosage and administration details:

Participants received placebo (0 mg/mL CBD) dissolved 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	Part B GWP42003-P 20 mg/kg/day Dose

Arm description:

Participants received 20 milligrams (mg) per kilogram (kg) per day of GWP42003-P 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	Cannibidiol, CBD, Epidiolex
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

GWP42003-P was presented an oral solution containing 100 mg/mL CBD dissolved 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	Part B Placebo

Arm description:

Participants received placebo (0 mg/mL CBD), volume-matched to the 20 mg/kg/day dose level, 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 of the matched dose) period.

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

Dosage and administration details:

Participants received placebo (0 mg/mL CBD) dissolved 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	Part A GWP42003-P 5 mg/kg/day Dose	Part A GWP42003-P 10 mg/kg/day Dose	Part A GWP42003-P 20 mg/kg/day Dose
Started	10	8	9
Safety Analysis Set	10	8	9
Completed	10	7	8
Not completed	0	1	1
Withdrawn by investigator	-	-	-
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	1	-
Met withdrawal criteria	-	-	1
Lost to follow-up	-	-	-

Number of subjects in period 1	Part A Placebo	Part B GWP42003-P 20 mg/kg/day Dose	Part B Placebo
Started	7	61	59
Safety Analysis Set	7	61	59
Completed	7	52	56
Not completed	0	9	3
Withdrawn by investigator	-	1	-
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	8	1
Met withdrawal criteria	-	-	-
Lost to follow-up	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part A GWP42003-P 5 mg/kg/day Dose
Reporting group description:	
Participants received GWP42003-P 5 milligrams per kilogram per day (mg/kg/day) administered orally, half in the morning and half in the evening. Participants titrated GWP42003-P to 5 mg/kg/day over 3 days and remained at this dose for the rest of the 21-day treatment period (19 days). The 21-day treatment period was followed by a 10-day taper (10% per day) period.	
Reporting group title	Part A 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 rest of the 21-day treatment period (15 days). The 21-day treatment period was followed by a 10-day taper (10% per day) period.	
Reporting group title	Part A GWP42003-P 20 mg/kg/day Dose
Reporting group description:	
Part A 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 rest of the 21-day treatment period (11 days). The 21-day treatment period was followed by a 10-day taper (10% per day) period.	
Reporting group title	Part A Placebo
Reporting group description:	
Participants received placebo (0 mg/mL CBD), volume-matched to one of the 3 dose levels (5, 10, or 20 mg/kg/day), administered orally, half in the morning and half in the evening for 21 days. To maintain the blinded aspect of the study, participants titrated the placebo dose over 3 to 11 days according to the matched investigational medicinal product (IMP) group (3, 7, and 11 days for the 5, 10, or 20 mg/kg/day GWP42003-P groups, respectively) and remained at this dose for the rest of the 21-day treatment period. The 21-day treatment period was followed by a 10-day taper (10% per day of the matched dose) period.	
Reporting group title	Part B GWP42003-P 20 mg/kg/day Dose
Reporting group description:	
Participants received 20 milligrams (mg) per kilogram (kg) per day of GWP42003-P 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	Part B Placebo
Reporting group description:	
Participants received placebo (0 mg/mL CBD), volume-matched to the 20 mg/kg/day dose level, 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 of the matched dose) period.	

Reporting group values	Part A GWP42003-P 5 mg/kg/day Dose	Part A GWP42003-P 10 mg/kg/day Dose	Part A GWP42003-P 20 mg/kg/day Dose
Number of subjects	10	8	9
Age categorical Units: Subjects			
Children (2-11 years)	10	8	9
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
Age continuous Units: years			
arithmetic mean	7.150	7.368	8.671

standard deviation	± 1.8955	± 2.1229	± 1.7957

Gender categorical Units: Subjects			
Female	5	5	6
Male	5	3	3

Reporting group values	Part A Placebo	Part B GWP42003-P 20 mg/kg/day Dose	Part B Placebo
Number of subjects	7	61	59
Age categorical Units: Subjects			
Children (2-11 years)	7	38	38
Adolescents (12-17 years)	0	22	19
Adults (18-64 years)	0	1	2
Age continuous Units: years			
arithmetic mean	6.978	9.736	9.779
standard deviation	± 0.9476	± 4.7309	± 4.8505
Gender categorical Units: Subjects			
Female	2	26	32
Male	5	35	27

Reporting group values	Total		
Number of subjects	154		
Age categorical Units: Subjects			
Children (2-11 years)	110		
Adolescents (12-17 years)	41		
Adults (18-64 years)	3		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	76		
Male	78		

End points

End points reporting groups

Reporting group title	Part A GWP42003-P 5 mg/kg/day Dose

Reporting group description:

Participants received GWP42003-P 5 milligrams per kilogram per day (mg/kg/day) administered orally, half in the morning and half in the evening. Participants titrated GWP42003-P to 5 mg/kg/day over 3 days and remained at this dose for the rest of the 21-day treatment period (19 days). The 21-day treatment period was followed by a 10-day taper (10% per day) period.

Reporting group title	Part A 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 rest of the 21-day treatment period (15 days). The 21-day treatment period was followed by a 10-day taper (10% per day) period.

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

Reporting group description:

Part A 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 rest of the 21-day treatment period (11 days). The 21-day treatment period was followed by a 10-day taper (10% per day) period.

Reporting group title	Part A Placebo

Reporting group description:

Participants received placebo (0 mg/mL CBD), volume-matched to one of the 3 dose levels (5, 10, or 20 mg/kg/day), administered orally, half in the morning and half in the evening for 21 days. To maintain the blinded aspect of the study, participants titrated the placebo dose over 3 to 11 days according to the matched investigational medicinal product (IMP) group (3, 7, and 11 days for the 5, 10, or 20 mg/kg/day GWP42003-P groups, respectively) and remained at this dose for the rest of the 21-day treatment period. The 21-day treatment period was followed by a 10-day taper (10% per day of the matched dose) period.

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

Reporting group description:

Participants received 20 milligrams (mg) per kilogram (kg) per day of GWP42003-P 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	Part B Placebo

Reporting group description:

Participants received placebo (0 mg/mL CBD), volume-matched to the 20 mg/kg/day dose level, 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 of the matched dose) period.

Primary: Part A: Number Of Participants Who Experienced Severe Treatment-Emergent Adverse Events (TEAEs)

End point title	Part A: Number Of Participants Who Experienced Severe Treatment-Emergent Adverse Events (TEAEs)[1][2]

End point description:

A TEAE was defined as an AE with an onset date on or after the first dose of investigational medicinal product (IMP). If an AE had a partial onset date and it was unclear from the partial date (or the stop date) whether the AE started prior to or following the first dose of IMP then the AE was considered a TEAE. The number of participants who experienced one or more severe TEAEs after dosing on Day 1 through the Safety Follow-up Visit (Day 60) is shown.
A summary of serious and all other non-serious AEs regardless of causality is located in the Adverse Events module.

End point type	Primary

End point timeframe:

Baseline (Day 1) through Safety follow-up visit (Day 60)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Quantitative statistical analyses were not performed on safety endpoints for Part A of the study.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint provides data for Part A of the study only. Severe TEAE data are not presented for Part B.

End point values	Part A GWP42003-P 5 mg/kg/day Dose	Part A GWP42003-P 10 mg/kg/day Dose	Part A GWP42003-P 20 mg/kg/day Dose	Part A Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	8	9	7
Units: Participants	2	1	0	1

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Percentage Change From Baseline In Convulsive Seizure Frequency During The Treatment Period

End point title	Part B: Percentage Change From Baseline In Convulsive Seizure Frequency During The Treatment Period[3]

End point description:

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

End point type	Primary

End point timeframe:

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

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint provides data for Part B of the study only. Change in convulsive seizure frequency data are not presented for Part A.

End point values	Part B GWP42003-P 20 mg/kg/day Dose	Part B Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	59		
Units: Percent change				
median (inter-quartile range (Q1-Q3))	-38.94 (-69.53 to -4.83)	-13.29 (-52.53 to 20.20)		

Statistical analyses

Statistical analysis title	GWP42003-P 20 mg/kg/Day Dose, Placebo
Comparison groups	Part B GWP42003-P 20 mg/kg/day Dose v Part B Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0123 [4]
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	-22.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.06
upper limit	-5.43

Notes:

[4] - The Wilcoxon test was used to calculate the p value, while the point estimate and confidence intervals were calculated using the Hodges–Lehmann approach.

Secondary: Part A: Area Under The Concentration-Time Curve Calculated To The Last Observable Concentration At Time T (AUC0-t) For CBD And Its Metabolites At Days 1 And 22

End point title	Part A: Area Under The Concentration-Time Curve Calculated To The Last Observable Concentration At Time T (AUC0-t) For CBD And Its Metabolites At Days 1 And 22[5]

End point description:

AUC0-t for CBD and its major metabolites, 6-hydroxy-CBD (6-OH-CBD), 7-hydroxy-CBD (7-OH-CBD), and 7-carboxy-cannabidiol (7-COOH-CBD) were calculated using blood samples collected before and after IMP dosing on Days 1 and 22. One sample was collected predose, 2 to 3 hours postdose, and 4 to 6 hours postdose for CBD and its metabolites. Results are presented for participants who received GWP42003-P at 5, 10, or 20 mg/kg/day during the study and for participants with a numeric result for the given evaluation. Data presented are geometric means (geometric coefficient of variation [%]).

End point type	Secondary

End point timeframe:

Predose and 2-6 hours postdose on Days 1 and 22

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint provides data for Part A of the study only. PK data are not presented for Part B.

End point values	Part A GWP42003-P 5 mg/kg/day Dose	Part A GWP42003-P 10 mg/kg/day Dose	Part A GWP42003-P 20 mg/kg/day Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[6]	8[7]	9[8]	
Units: hours*nanograms/mL				
geometric mean (geometric coefficient				

of variation)				
Day 1 CBD	70.61 (± 20.38)	66.35 (± 120.8)	73.69 (± 96.64)	
Day 22 CBD	240.8 (± 100.8)	721.8 (± 79.92)	962.6 (± 93.43)	
Day 1 6-OH-CBD	3.27 (± 132)	2.79 (± 87.7)	5.16 (± 57.2)	
Day 22 6-OH-CBD	9.33 (± 119)	26.3 (± 82.9)	58.6 (± 90.1)	
Day 1 7-OH-CBD	21.9 (± 57.0)	18.4 (± 299)	30.2 (± 105)	
Day 22 7-OH-CBD	131 (± 107)	244 (± 120)	508 (± 96.0)	
Day 1 7-COOH-CBD	297 (± 97.3)	125 (± 1750)	195 (± 573)	
Day 22 7-COOH-CBD	4190 (± 81.20)	9220 (± 178)	15500 (± 148)	

Notes:

[6] - CBD (Day 1) 5 (Day 22) 9
6-OH-CBD (1) 3 (22) 8
7-OH-CBD (1) 5 (22) 8
7-COOH-CBD (1) 6 (22) 9
[7] - CBD (Day 1) 7 (Day 22) 7
6-OH-CBD (1) 5 (22) 7
7-OH-CBD (1) 7 (22) 7
7-COOH-CBD (1) 6 (22) 5
[8] - CBD (Day 1) 7 (Day 22) 7
6-OH-CBD (1) 5 (22) 6
7-OH-CBD (1) 8 (22) 6
7-COOH-CBD (1) 6 (22) 5

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Mean Percentage Change From Baseline To End Of Treatment In Plasma Clobazam (CLB) And N-Desmethylclobazam (N-CLB) Concentrations

End point title	Part A: Mean Percentage Change From Baseline To End Of Treatment In Plasma Clobazam (CLB) And N-Desmethylclobazam (N-CLB) Concentrations[9]

End point description:

Plasma concentrations of CLB and N-CLB were measured on Days 1 and 22. Participants were instructed to take their daily dose of CLB 2 hours prior to the anticipated pre-IMP blood specimen collection on both days. Blood samples were collected prior to administration of IMP. Results are presented for a subgroup of participants who took CLB during the study and had PK samples analyzed at both pharmacokinetics (PK) sampling visits (Days 1 and 22).

End point type	Secondary

End point timeframe:

Predose on Days 1 and 22

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint provides data for Part A of the study only. CLB and N-CLB data are not presented for Part B.

End point values	Part A GWP42003-P 5 mg/kg/day Dose	Part A GWP42003-P 10 mg/kg/day Dose	Part A GWP42003-P 20 mg/kg/day Dose	Part A Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	5	5
Units: percent change				
number (not applicable)				
% change in CLB	-1.2	18.0	29.6	15.1
% change in N-CLB	258.7	170.7	228.9	-5.6

Statistical analyses

No statistical analyses for this end point

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

End point title	Part B: Number Of Participants With A ≥50% Reduction From Baseline In Convulsive Seizure Frequency During The Treatment Period[10]

End point description:

Convulsive seizures (atonic, clonic, tonic, or tonic-clonic) were recorded by the participant or caregiver using an IVRS diary. 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

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint provides data for Part B of the study only. Reduction in seizure frequency data are not presented for Part A.

End point values	Part B GWP42003-P 20 mg/kg/day Dose	Part B Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	59		
Units: Participants				
≥50% Reduction	26	16		

Statistical analyses

Statistical analysis title	GWP42003-P 20 mg/kg/Day Dose, Placebo
Comparison groups	Part B GWP42003-P 20 mg/kg/day Dose v Part B Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0784
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	4.3

Secondary: Part B: Number Of Participants with A ≥25%, ≥75%, Or 100% Reduction From Baseline In Convulsive Seizure Frequency During The Treatment Period

End point title	Part B: Number Of Participants with A ≥25%, ≥75%, Or 100% Reduction From Baseline In Convulsive Seizure Frequency During The Treatment Period[11]

End point description:

Convulsive seizures (atonic, clonic, tonic, or tonic-clonic) were recorded by the participant or caregiver using an 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

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint provides data for Part B of the study only. Convulsive seizure data are not presented for Part A.

End point values	Part B GWP42003-P 20 mg/kg/day Dose	Part B Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	59		
Units: Participants				
≥25% Reduction	38	26		
≥75% Reduction	14	7		
100% Reduction	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Percentage Change From Baseline In Non-Convulsive Seizure Frequency During The Treatment Period

End point title	Part B: Percentage Change From Baseline In Non-Convulsive Seizure Frequency During The Treatment Period[12]

End point description:

Non-convulsive seizures (myoclonic, partial, or absence) were recorded by the participant or caregiver using an IVRS diary. Percentage change from baseline was calculated as per the primary outcome measure. Only participants with non-convulsive seizures during the baseline period were included. Negative percentages show an improvement from baseline.

End point type	Secondary

End point timeframe:

Baseline to EOT (Day 99) or ET

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint provides data for Part B of the study only. Non-convulsive seizure frequency data are not presented for Part A.

End point values	Part B GWP42003-P 20 mg/kg/day Dose	Part B Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	41		
Units: Percent change				
median (inter-quartile range (Q1-Q3))	-40.16 (-92.1 to -3.6)	-34.69 (-97.5 to -0.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Caregiver Global Impression Of Change In Seizure Duration (CGICSD)

End point title	Part B: Caregiver Global Impression Of Change In Seizure Duration (CGICSD)[13]

End point description:

Seizure duration was assessed qualitatively using the CGICSD. Caregivers were asked "Since the patient started treatment, please assess the average duration of the patient's seizures (comparing their condition now to their condition before treatment)"; responses included decrease, no change, or increase in average duration. For each seizure type, only participants with at least 1 seizure for the corresponding seizure type, reported at any time during the study, were included.

End point type	Secondary

End point timeframe:

Baseline to EOT (Day 99) or ET

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint provides data for Part B of the study only. Duration of seizure subtype data are not presented for Part A.

End point values	Part B GWP42003-P 20 mg/kg/day Dose	Part B Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	59		
Units: Participants				
Tonic-Clonic Seizures Number Analyzed	49	41		
Tonic-Clonic Seizures Decrease in average duration	17	8		
Tonic-Clonic Seizures No change in aver. duration	32	31		

Tonic-Clonic Seizures Increase in average duration	0	2		
Tonic Seizures Number Analyzed	12	15		
Tonic Seizures Decrease in average duration	4	2		
Tonic Seizures No change in average duration	8	12		
Tonic Seizures Increase in average duration	0	1		
Clonic Seizures Number Analyzed	11	7		
Clonic Seizures Decrease in average duration	5	3		
Clonic Seizures No change in average duration	6	3		
Clonic Seizures Increase in average duration	0	1		
Atonic Seizures Number Analyzed	3	7		
Atonic Seizures Decrease in average duration	2	2		
Atonic Seizures No change in average duration	1	3		
Atonic Seizures Increase in average duration	0	2		
Myoclonic Seizures Number Analyzed	14	18		
Myoclonic Seizures Decrease in average duration	4	3		
Myoclonic Seizures No change in average duration	10	12		
Myoclonic Seizures Increase in average duration	0	3		
Countable Partial Seizures Number Analyzed	12	13		
Countable Partial Seizures Decrease in aver. dur.	5	2		
Countable Partial Seizures No change in aver. dur.	7	9		
Countable Partial Seizures Increase in aver. dur.	0	2		
Other Partial Seizures Number Analyzed	3	5		
Other Partial Seizures Decrease in aver. dur.	0	3		
Other Partial Seizures No change in aver. dur.	3	2		
Other Partial Seizures Increase in aver. dur.	0	0		
Absence Seizures Number Analyzed	16	19		
Absence Seizures Decrease in average duration	4	6		
Absence Seizures No change in average duration	11	12		
Absence Seizures Increase in average duration	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number Of Participants Using Rescue Medication

End point title	Part B: Number Of Participants Using Rescue Medication[14]

End point description:

The use of rescue medication was recorded by the participant or caregiver using a paper diary.

End point type	Secondary

End point timeframe:

Baseline to EOT (Day 99) or ET

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint provides data for Part B of the study only. Rescue medication data are not presented for Part A.

End point values	Part B GWP42003-P 20 mg/kg/day Dose	Part B Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	59		
Units: Participants	36	41		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number Of Participants With Inpatient Hospitalizations Due To Epilepsy

End point title	Part B: Number Of Participants With Inpatient Hospitalizations Due To Epilepsy[15]

End point description:

Inpatient hospitalizations due to epilepsy were recorded by the participant or caregiver and through the serious adverse events (SAE) reporting process.

End point type	Secondary

End point timeframe:

Baseline to Safety Follow-up (Day 137)

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint provides data for Part A of the study only. Hospitalization data are not presented for Part B.

End point values	Part B GWP42003-P 20 mg/kg/day Dose	Part B Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	59		
Units: Participants				
Caregiver/participant-reported	5	1		
Investigator-reported (serious TEAE)	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change From Baseline In Sleep Disruption 0 To 10 Numerical Rating Scale (0 to 10 NRS) Score

End point title	Part B: Change From Baseline In Sleep Disruption 0 To 10 Numerical Rating Scale (0 to 10 NRS) Score[16]

End point description:

The sleep disruption 0 to 10 NRS questionnaire was completed by the participant's caregiver. The caregiver was asked 'On a scale of '0 to 10', please indicate the number that best describes your child's sleep disruption in the last week.' The markers ranged from 0 = 'slept extremely well' to 10 = 'unable to sleep at all'. The change from baseline in the sleep disruption 0 to 10 numerical rating scale score was analyzed using an analysis of covariance (ANCOVA) model with baseline and age group (2 to 5 years, 6 to 12 years and 13 to 18 years) as covariates and treatment group as a fixed factor. A negative change from baseline represents an improvement in sleep. 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

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint provides data for Part B of the study only. Change In Sleep Disruption NRS data are not presented for Part A.

End point values	Part B GWP42003-P 20 mg/kg/day Dose	Part B Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	59		
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.7 (-1.5 to 0.1)	-0.3 (-1.1 to 0.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change From Baseline In Epworth Sleepiness Scale (ESS) Score

End point title	Part B: Change From Baseline In Epworth Sleepiness Scale (ESS) Score[17]

End point description:

The ESS questionnaire was completed by the participant's caregiver. The change from baseline in the ESS score was analyzed using an ANCOVA model with baseline and age group (2 to 5 years, 6- to 2

years and 13 to 18 years) as covariates and treatment group as a fixed factor. The total score was the sum of the 8 item-scores and ranged from 0 to 24. A higher total score represents greater levels of daytime sleepiness.

End point type	Secondary

End point timeframe:

Baseline to Last Visit (Day 99) or ET

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint provides data for Part B of the study only. ESS data are not presented for Part A.

End point values	Part B GWP42003-P 20 mg/kg/day Dose	Part B Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	58		
Units: units on a scale				
least squares mean (confidence interval 95%)	0.82 (-0.36 to 1.99)	-0.69 (-1.90 to 0.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change From Baseline In Quality Of Life In Childhood Epilepsy (QOLCE) Score

End point title	Part B: Change From Baseline In Quality Of Life In Childhood Epilepsy (QOLCE) Score[18]

End point description:

The QOLCE questionnaire was completed by the parent or caregiver of participants aged 4 years and above. The change from baseline in the overall quality of life score was analyzed using an ANCOVA model with baseline and age group (2 to 5 years, 6 to 12 years and 13 to 18 years) as covariates and treatment group as a fixed factor. Zero represents the lowest or poorest category and 100 represents the highest level of functioning. The overall quality of life score was calculated by taking the mean of the subscale scores.

End point type	Secondary

End point timeframe:

Baseline to EOT (Day 99)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Quantitative statistical analyses were not performed for this endpoint. Descriptive statistics are presented.

End point values	Part B GWP42003-P 20 mg/kg/day Dose	Part B Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: units on a scale				
least squares mean (confidence interval	5.6 (1.9 to 9.3)	4.1 (0.2 to 8.0)		

95%)

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change From Baseline In Vineland Adaptive Behavior Scales, Second Edition (Vineland-II) Score

End point title	Part B: Change From Baseline In Vineland Adaptive Behavior Scales, Second Edition (Vineland-II) Score[19]

End point description:

The Vineland-II scores (standard scores and adaptive levels for each adaptive behavior domain, the adaptive behavior composite, and the maladaptive behavior index score and level) were assessed by the participant's caregiver. Scores were analyzed using an ANCOVA model with baseline and age group (2 to 5 years, 6 to 12 years, and 13 to 18 years) as covariates and treatment group as a fixed factor. Higher scores represent greater levels of functioning except for the maladaptive behavior index, for which a negative change from baseline represents an improvement in condition.

End point type	Secondary

End point timeframe:

Baseline to Last Visit (Day 99) or ET

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint provides data for Part B of the study only. Vineland Adaptive Behavior Scale data are not presented for Part A.

End point values	Part B GWP42003-P 20 mg/kg/day Dose	Part B Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61[20]	59[21]		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Communication Domain Standard Score	-0.8 (-3.2 to 1.5)	3.0 (0.8 to 5.3)		
Daily Living Skills Domain Standard Score	-0.8 (-4.0 to 2.4)	-0.8 (-4.1 to 2.6)		
Socialization Domain Standard Score	-0.6 (-4.6 to 3.5)	-0.6 (-4.0 to 2.7)		
Motor Skills Domain Standard Score	-2.5 (-5.5 to 0.5)	1.7 (-1.1 to 4.5)		
Adaptive Behavior Composite Standard Score	-2.0 (-5.2 to 1.1)	0.6 (-2.1 to 3.3)		
Maladaptive Behavior Index v-Scale Score	-0.3 (-0.7 to 0.1)	-0.4 (-0.8 to 0.0)		

Notes:

[20] - Numbers Analysed
CDSS 17
DLSDSS 20
SDSS 12
MSDSS 20
ABCSS 12

MBIvSS 47

[21] - Numbers Analysed
CDSS 19
DLSDSS 19
SDSS 16
MSDSS 22
ABCSS 15
MBIvSS 48

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Caregiver Global Impression Of Change (CGIC)

End point title	Part B: Caregiver Global Impression Of Change (CGIC)[22]

End point description:

The 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 CGIC questionnaire at subsequent visits.

End point type	Secondary

End point timeframe:

Baseline to Last Visit (Day 99) or ET

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint provides data for Part B of the study only. CGIC data are not presented for Part A.

End point values	Part B GWP42003-P 20 mg/kg/day Dose	Part B Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	58		
Units: Participants				
Very Much Improved	9	4		
Much Improved	10	4		
Slightly Improved	18	12		
No Change	15	31		
Slightly Worse	3	6		
Much Worse	4	1		
Very Much Worse	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline (Day 1) up to Day 60 (Part A) or Day 137 (Part B)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Part A GWP42003-P 5 mg/kg/day Dose

Reporting group description:

Participants received GWP42003-P 5 mg/kg/day administered orally, half in the morning and half in the evening. Participants titrated GWP42003-P to 5 mg/kg/day over 3 days and remained at this dose for the rest of the 21-day treatment period (19 days). The 21-day treatment period was followed by a 10-day taper (10% per day) period.

Reporting group title	Part A 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 rest of the 21-day treatment period (15 days). The 21-day treatment period was followed by a 10-day taper (10% per day) period.

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

Reporting group description:

Part A 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 rest of the 21-day treatment period (11 days). The 21-day treatment period was followed by a 10-day taper (10% per day) period.

Reporting group title	Part A Placebo

Reporting group description:

Participants received placebo (0 mg/mL CBD), volume matched to one of the 3 dose levels (5, 10, or 20 mg/kg/day), administered orally, half in the morning and half in the evening for 21 days. To maintain the blinded aspect of the study, participants titrated the placebo dose over 3 to 11 days according to the matched IMP group (3, 7, and 11 days for the 5, 10, or 20 mg/kg/day GWP42003-P groups, respectively) and remained at this dose for the rest of the 21-day treatment period. The 21-day treatment period was followed by a 10-day taper (10% per day of the matched dose) period.

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

Reporting group description:

Participants received 20 milligrams (mg) per kilogram (kg) per day of GWP42003-P 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	Part B Placebo

Reporting group description:

Participants received placebo (0 mg/mL CBD), volume-matched to the 20 mg/kg/day dose level, 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 of the matched dose) period.

Serious adverse events	Part A GWP42003-P 5 mg/kg/day Dose	Part A GWP42003-P 10 mg/kg/day Dose	Part A GWP42003-P 20 mg/kg/day Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	2 / 8 (25.00%)	1 / 9 (11.11%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			

subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 9 (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
Status Epilepticus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (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
Hypotonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myoclonus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	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	0 / 10 (0.00%)	2 / 8 (25.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			

subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash Maculo-papular			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 9 (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
Infections and infestations			
Parvovirus Infection			

subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral Infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophagia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part A Placebo	Part B GWP42003-P 20 mg/kg/day Dose	Part B Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	10 / 61 (16.39%)	3 / 59 (5.08%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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
Gamma-glutamyltransferase			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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
Platelet count			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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
Weight decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 7 (14.29%)	2 / 61 (3.28%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status Epilepticus			

subjects affected / exposed	0 / 7 (0.00%)	3 / 61 (4.92%)	3 / 59 (5.08%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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
Lethargy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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
Myoclonus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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	0 / 7 (0.00%)	3 / 61 (4.92%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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			

Abdominal distension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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 haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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			
Epistaxis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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 failure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash Maculo-papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Parvovirus Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral Infection			

subjects affected / exposed	1 / 7 (14.29%)	0 / 61 (0.00%)	0 / 59 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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
Oral herpes			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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
Hypophagia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (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	Part A GWP42003-P 5 mg/kg/day Dose	Part A GWP42003-P 10 mg/kg/day Dose	Part A GWP42003-P 20 mg/kg/day Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 10 (80.00%)	5 / 8 (62.50%)	7 / 9 (77.78%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1

Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Hepatic enzyme increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Liver function test abnormal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Urine ketone body absent			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Urine ketone body present			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Ataxia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	2	0	1
Convulsion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Coordination abnormal			

subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Dysarthria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Poor quality sleep			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Psychomotor hyperactivity			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Sedation			
subjects affected / exposed	2 / 10 (20.00%)	0 / 8 (0.00%)	2 / 9 (22.22%)
occurrences (all)	2	0	2
Somnolence			
subjects affected / exposed	2 / 10 (20.00%)	3 / 8 (37.50%)	0 / 9 (0.00%)
occurrences (all)	2	3	0
Tremor			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Gait disturbance			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			

subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	3 / 10 (30.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	3	1	0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Constipation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Dry Mouth			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Eructation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Haematochezia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	1 / 8 (12.50%)	1 / 9 (11.11%)
occurrences (all)	1	1	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			

Dermatitis diaper			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Rash papular			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	3 / 10 (30.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Irritability			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Mood swings			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Erythema infectiosum			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis viral			

subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Lower respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Otitis media acute			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pharyngitis streptococcal			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	1 / 9 (11.11%)
occurrences (all)	0	1	2
Upper respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Viral rash			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	4 / 9 (44.44%)
occurrences (all)	0	1	4
Increased appetite			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Ketosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Part A Placebo	Part B GWP42003-P 20 mg/kg/day Dose	Part B Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	46 / 61 (75.41%)	28 / 59 (47.46%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 7 (14.29%)	1 / 61 (1.64%)	0 / 59 (0.00%)
occurrences (all)	1	1	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
Liver function test abnormal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	1 / 59 (1.69%)
occurrences (all)	0	1	1
Urine ketone body absent			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
Urine ketone body present			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	4 / 61 (6.56%)	0 / 59 (0.00%)
occurrences (all)	0	4	0
Transaminases increased			
subjects affected / exposed	0 / 7 (0.00%)	4 / 61 (6.56%)	0 / 59 (0.00%)
occurrences (all)	0	4	0
Weight decreased			
subjects affected / exposed	0 / 7 (0.00%)	4 / 61 (6.56%)	0 / 59 (0.00%)
occurrences (all)	0	4	0
Injury, poisoning and procedural complications			
Accident			

subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 61 (3.28%)	0 / 59 (0.00%)
occurrences (all)	0	2	0
Convulsion			
subjects affected / exposed	1 / 7 (14.29%)	5 / 61 (8.20%)	2 / 59 (3.39%)
occurrences (all)	1	5	3
Coordination abnormal			
subjects affected / exposed	0 / 7 (0.00%)	2 / 61 (3.28%)	0 / 59 (0.00%)
occurrences (all)	0	2	0
Dysarthria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	0 / 59 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	3 / 59 (5.08%)
occurrences (all)	0	1	5
Poor quality sleep			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
Psychomotor hyperactivity			
subjects affected / exposed	1 / 7 (14.29%)	2 / 61 (3.28%)	2 / 59 (3.39%)
occurrences (all)	1	2	2
Sedation			
subjects affected / exposed	0 / 7 (0.00%)	2 / 61 (3.28%)	0 / 59 (0.00%)
occurrences (all)	0	2	0
Somnolence			
subjects affected / exposed	1 / 7 (14.29%)	19 / 61 (31.15%)	6 / 59 (10.17%)
occurrences (all)	1	23	13
Tremor			
subjects affected / exposed	0 / 7 (0.00%)	2 / 61 (3.28%)	0 / 59 (0.00%)
occurrences (all)	0	2	0
Lethargy			
subjects affected / exposed	0 / 7 (0.00%)	7 / 61 (11.48%)	3 / 59 (5.08%)
occurrences (all)	0	9	4

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 7 (28.57%)	11 / 61 (18.03%)	2 / 59 (3.39%)
occurrences (all)	2	12	2
Gait disturbance			
subjects affected / exposed	0 / 7 (0.00%)	3 / 61 (4.92%)	0 / 59 (0.00%)
occurrences (all)	0	3	0
Influenza like illness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	9 / 61 (14.75%)	5 / 59 (8.47%)
occurrences (all)	0	13	7
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	2 / 59 (3.39%)
occurrences (all)	0	1	2
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	19 / 61 (31.15%)	6 / 59 (10.17%)
occurrences (all)	1	33	8
Dry Mouth			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
Eructation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0

Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	9 / 61 (14.75%)	3 / 59 (5.08%)
occurrences (all)	0	13	5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 7 (14.29%)	4 / 61 (6.56%)	2 / 59 (3.39%)
occurrences (all)	1	4	3
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	1 / 7 (14.29%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 7 (0.00%)	2 / 61 (3.28%)	1 / 59 (1.69%)
occurrences (all)	0	3	1
Rash papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	1 / 59 (1.69%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 7 (0.00%)	2 / 61 (3.28%)	1 / 59 (1.69%)
occurrences (all)	0	2	1
Irritability			
subjects affected / exposed	0 / 7 (0.00%)	4 / 61 (6.56%)	0 / 59 (0.00%)
occurrences (all)	0	6	0
Mood swings			
subjects affected / exposed	1 / 7 (14.29%)	1 / 61 (1.64%)	0 / 59 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Proteinuria			

subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Erythema infectiosum			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	2 / 7 (28.57%)	2 / 61 (3.28%)	0 / 59 (0.00%)
occurrences (all)	2	2	0
Gastroenteritis viral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	3 / 61 (4.92%)	3 / 59 (5.08%)
occurrences (all)	1	3	3
Otitis media acute			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0
Pharyngitis streptococcal			
subjects affected / exposed	1 / 7 (14.29%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 61 (1.64%)	1 / 59 (1.69%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	7 / 61 (11.48%)	5 / 59 (8.47%)
occurrences (all)	0	7	6
Viral infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	2 / 59 (3.39%)
occurrences (all)	0	0	2
Viral rash			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)	16 / 61 (26.23%)	3 / 59 (5.08%)
occurrences (all)	0	21	3
Increased appetite			
subjects affected / exposed	0 / 7 (0.00%)	3 / 61 (4.92%)	0 / 59 (0.00%)
occurrences (all)	0	3	0
Ketosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 61 (0.00%)	0 / 59 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2014	Clarification of trial procedures, including the following -Added CGICSD as a secondary assessment and analysis of major metabolites of CBD. -Added a pre-randomization pregnancy test. -Clarified exclusion criteria related to previous use of cannabinoids. -Clarified study procedures, including collection of seizure information for Part A, IMP usage, rescue medication, concomitant anti-epilepsy drugs, and AEs for parts A and B; collection of epilepsy-specific genetic testing and prior anti-epileptic drugs; capturing seizure information and IMP supply; timing of CLB administration -Clarified baseline and safety follow-up periods and visit windows as well as time periods for safety calls and completing case report forms and collection of epilepsy-related hospitalization information -Clarified seizure types and subtypes -Clarified that any AE or drug-induced liver injury could be reason for withdrawal -Clarified when diary information would be collected -Clarified when the taper period would start for participants who terminated early -Added use of diagnostic review and clarified the qualifications for administering the C-SSRS -Clarified when seizures were considered AEs and when AEs should be reviewed by the DSMC
29 May 2015	Clarification of trial procedures, including the following: -Revision of endpoint analyses, including Part B primary and secondary endpoints to use the full treatment period (which included titration and maintenance periods); definition of "baseline" for statistical analyses; seizure frequency used in the sensitivity analysis for Part B, new sensitivity analyses for Part B; and details on multiple imputation methods for sensitivity analyses for the primary endpoint in Part B. -Revision/clarification of procedures, including Tanner staging age; monitoring of potential cases of DILI, alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase levels until normalized; monitoring of the plasma concentration of concomitant anti-epilepsy drugs and dosage modification if concentrations are altered following administration of IMP; instructions for follow-up for elevated liver enzymes that were not considered DILI; clarification regarding who may participate in the C-SSRS; and collection of seizure count information for Part B. -Clarified assessments including effects of IMP on menstruation cycles and measuring plasma concentrations of anti-epilepsy drugs. -Clarification that only convulsive seizures in the first 28 days of the baseline period would count toward eligibility.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In Part A, there were analytical issues for 7-OH-CBD related to reference material batch used during analysis. Data are qualitative.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29540584

http://www.ncbi.nlm.nih.gov/pubmed/28538134