Clinical trial results:
A double blind, randomized, placebo-controlled, two-part study to investigate the pharmacokinetics, followed by efficacy and safety of GWP42006 as add-on therapy in patients with inadequately controlled focal seizures.

Summary

EudraCT number	2014-002594-11
Trial protocol	GB CZ ES HU
Global end of trial date	01 September 2017

Results information

Result version number	v1 (current)
This version publication date	15 February 2019
First version publication date	15 February 2019

Trial information

Trial identification

Sponsor protocol code	GWEP1330

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	NCT Number (Part A): NCT02369471, NCT Number (Part B): NCT02365610

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. Switchboard, GW Research Ltd., +44 1223266800, info@gwpharm.com
Scientific contact	GW Research Ltd. Switchboard, GW Research Ltd., +44 1223266800, info@gwpharm.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2017
Global end of trial reached?	Yes
Global end of trial date	01 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part A: To determine the pharmacokinetics of GWP42006 and human metabolites, 7-hydroxy-cannabidivarin (7-OH-CBDV) and 6-hydroxy-cannabidivarin (6-OH-CBDV), in the presence of other antiepileptic drugs (AEDs). To evaluate the safety and tolerability of GWP42006 compared with placebo, in the presence of other AEDs. To evaluate the effects of GWP42006 on plasma concentrations of concomitant AEDs.
Part B: To evaluate the efficacy of GWP42006, compared with placebo, as add-on therapy to treat inadequately controlled focal seizures.

Protection of trial subjects:

This trial 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 trial is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 98
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	Czech Republic: 32
Country: Number of subjects enrolled	Hungary: 24
Worldwide total number of subjects	194
EEA total number of subjects	194

Notes:

Subjects enrolled per age group

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

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	194
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This trial consisted of 2 parts. Part A included participants who had focal seizures despite prior treatment with at least 2 AEDs and who were currently taking 1 to 3 AEDs. Part B included participants who had well-documented histories of focal seizures despite prior treatment with at least 2 AEDs and who were currently taking 1 to 3 AEDs.

Period 1

Period 1 title	Parts A and B Combined (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

The study drug was provided in a packed and labelled state. Following randomization, participants were allocated a prepacked, numbered study drug. The identity of the study drug assigned to participants was held by an interactive voice response system.

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: GWP42006, 400 mg twice daily

Arm description:

Part A consisted of a 2-week baseline period and a 2-week treatment period. Participants were required to attend 6 trial visits, with a follow-up call 4 weeks after the last dose of study drug. GWP42006 was taken orally, 400 milligrams (mg) twice daily for 2 weeks, by participants who were categorized into 1 of 3 groups according to their concomitant AED regimen at trial entry. Group 1 included participants who took inducer AEDs (carbamazepine, phenobarbital, primidone, or phenytoin), but did not take inhibitor AEDs (valproic acid). Group 2 included participants who took inhibitor AEDs (valproic acid), but who did not take inducer AEDs (carbamazepine, phenobarbital, primidone, or phenytoin). Group 3 included participants on AEDs that were neither inducers nor inhibitors.

Arm type	Experimental
Investigational medicinal product name	GWP42006
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

GWP42006 was taken orally as an oral solution containing 50 mg/milliliter (mL) CBDV dissolved in the excipients sesame oil and anhydrous ethanol (79 mg/mL) with added sweetener (sucralose 0.5 mg/mL) and strawberry flavoring (0.2 mg/mL).

Arm title	Part A: Placebo, 400 mg twice daily

Arm description:

Part A consisted of a 2-week baseline period and a 2-week treatment period. Participants were required to attend 6 trial visits, with a follow-up call 4 weeks after the last dose of study drug. Placebo was taken orally, 400 mg twice daily for 2 weeks, by participants who were categorized into 1 of 3 groups according to their concomitant AED regimen at trial entry. Group 1 included participants who took inducer AEDs (carbamazepine, phenobarbital, primidone, or phenytoin), but did not take inhibitor AEDs (valproic acid). Group 2 included participants who took inhibitor AEDs (valproic acid), but who did not take inducer AEDs (carbamazepine, phenobarbital, primidone, or phenytoin). Group 3 included participants on AEDs that were neither inducers nor inhibitors.

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:

Placebo oral solution contained the excipients sesame oil (0 mg/mL CBDV) and anhydrous ethanol (79 mg/mL) with added sweetener (sucralose, 0.5 mg/mL) and strawberry flavoring (0.2 mg/mL).

Arm title	Part B: GWP42006, 800 mg twice daily

Arm description:

Part B consisted of a 4-week baseline period, a 2-week dose-escalation period, a 6-week stable treatment period, and a 12-day taper period. GWP42006 was taken orally, 800 mg twice daily, for approximately 10 weeks. Participants were required to attend 8 trial visits, with a follow-up call 4 weeks after the last dose.

Arm type	Experimental
Investigational medicinal product name	GWP42006
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

GWP42006 was taken orally as an oral solution containing 50 mg/mL CBDV dissolved in the excipients sesame oil and anhydrous ethanol (79 mg/mL) with added sweetener (sucralose 0.5 mg/mL) and strawberry flavoring (0.2 mg/mL).

Arm title	Part B: Placebo, 800 mg twice daily

Arm description:

Part B consisted of a 4-week baseline period, a 2-week dose-escalation period, a 6-week stable treatment period, and a 12-day taper period. Placebo was taken orally, 800 mg twice daily, for approximately 10 weeks. Participants were required to attend 8 trial visits, with a follow-up call 4 weeks after the last dose.

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:

Placebo oral solution contained the excipients sesame oil (0 mg/mL CBDV) and anhydrous ethanol (79 mg/mL) with added sweetener (sucralose, 0.5 mg/mL) and strawberry flavoring (0.2 mg/mL).

Number of subjects in period 1	Part A: GWP42006, 400 mg twice daily	Part A: Placebo, 400 mg twice daily	Part B: GWP42006, 800 mg twice daily
Started	26	6	81
Received At Least 1 Dose Of Study Drug	26	6	81
Completed	26	6	65
Not completed	0	0	16
Consent withdrawn by subject	-	-	5
Adverse event, non-fatal	-	-	9
Protocol deviation	-	-	1
Met Withdrawal Criteria	-	-	1

Number of subjects in period 1	Part B: Placebo, 800 mg twice daily
Started	81
Received At Least 1 Dose Of Study Drug	81
Completed	77
Not completed	4
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Protocol deviation	1
Met Withdrawal Criteria	-

Baseline characteristics

Reporting groups	
Reporting group title	Part A: GWP42006, 400 mg twice daily
Reporting group description:	
Part A consisted of a 2-week baseline period and a 2-week treatment period. Participants were required to attend 6 trial visits, with a follow-up call 4 weeks after the last dose of study drug. GWP42006 was taken orally, 400 milligrams (mg) twice daily for 2 weeks, by participants who were categorized into 1 of 3 groups according to their concomitant AED regimen at trial entry. Group 1 included participants who took inducer AEDs (carbamazepine, phenobarbital, primidone, or phenytoin), but did not take inhibitor AEDs (valproic acid). Group 2 included participants who took inhibitor AEDs (valproic acid), but who did not take inducer AEDs (carbamazepine, phenobarbital, primidone, or phenytoin). Group 3 included participants on AEDs that were neither inducers nor inhibitors.	
Reporting group title	Part A: Placebo, 400 mg twice daily
Reporting group description:	
Part A consisted of a 2-week baseline period and a 2-week treatment period. Participants were required to attend 6 trial visits, with a follow-up call 4 weeks after the last dose of study drug. Placebo was taken orally, 400 mg twice daily for 2 weeks, by participants who were categorized into 1 of 3 groups according to their concomitant AED regimen at trial entry. Group 1 included participants who took inducer AEDs (carbamazepine, phenobarbital, primidone, or phenytoin), but did not take inhibitor AEDs (valproic acid). Group 2 included participants who took inhibitor AEDs (valproic acid), but who did not take inducer AEDs (carbamazepine, phenobarbital, primidone, or phenytoin). Group 3 included participants on AEDs that were neither inducers nor inhibitors.	
Reporting group title	Part B: GWP42006, 800 mg twice daily
Reporting group description:	
Part B consisted of a 4-week baseline period, a 2-week dose-escalation period, a 6-week stable treatment period, and a 12-day taper period. GWP42006 was taken orally, 800 mg twice daily, for approximately 10 weeks. Participants were required to attend 8 trial visits, with a follow-up call 4 weeks after the last dose.	
Reporting group title	Part B: Placebo, 800 mg twice daily
Reporting group description:	
Part B consisted of a 4-week baseline period, a 2-week dose-escalation period, a 6-week stable treatment period, and a 12-day taper period. Placebo was taken orally, 800 mg twice daily, for approximately 10 weeks. Participants were required to attend 8 trial visits, with a follow-up call 4 weeks after the last dose.	

Reporting group values	Part A: GWP42006, 400 mg twice daily	Part A: Placebo, 400 mg twice daily	Part B: GWP42006, 800 mg twice daily
Number of subjects	26	6	81
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	26	6	81
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	45.1	41.6	36.0
standard deviation	± 12.59	± 13.84	± 10.61

Gender categorical Units: Subjects			
Female	16	4	47
Male	10	2	34

Reporting group values	Part B: Placebo, 800 mg twice daily	Total	
Number of subjects	81	194	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	81	194	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	36.1		
standard deviation	± 12.84	-	
Gender categorical Units: Subjects			
Female	43	110	
Male	38	84	

End points

End points reporting groups

Reporting group title	Part A: GWP42006, 400 mg twice daily

Reporting group description:

Part A consisted of a 2-week baseline period and a 2-week treatment period. Participants were required to attend 6 trial visits, with a follow-up call 4 weeks after the last dose of study drug. GWP42006 was taken orally, 400 milligrams (mg) twice daily for 2 weeks, by participants who were categorized into 1 of 3 groups according to their concomitant AED regimen at trial entry. Group 1 included participants who took inducer AEDs (carbamazepine, phenobarbital, primidone, or phenytoin), but did not take inhibitor AEDs (valproic acid). Group 2 included participants who took inhibitor AEDs (valproic acid), but who did not take inducer AEDs (carbamazepine, phenobarbital, primidone, or phenytoin). Group 3 included participants on AEDs that were neither inducers nor inhibitors.

Reporting group title	Part A: Placebo, 400 mg twice daily

Reporting group description:

Part A consisted of a 2-week baseline period and a 2-week treatment period. Participants were required to attend 6 trial visits, with a follow-up call 4 weeks after the last dose of study drug. Placebo was taken orally, 400 mg twice daily for 2 weeks, by participants who were categorized into 1 of 3 groups according to their concomitant AED regimen at trial entry. Group 1 included participants who took inducer AEDs (carbamazepine, phenobarbital, primidone, or phenytoin), but did not take inhibitor AEDs (valproic acid). Group 2 included participants who took inhibitor AEDs (valproic acid), but who did not take inducer AEDs (carbamazepine, phenobarbital, primidone, or phenytoin). Group 3 included participants on AEDs that were neither inducers nor inhibitors.

Reporting group title	Part B: GWP42006, 800 mg twice daily

Reporting group description:

Part B consisted of a 4-week baseline period, a 2-week dose-escalation period, a 6-week stable treatment period, and a 12-day taper period. GWP42006 was taken orally, 800 mg twice daily, for approximately 10 weeks. Participants were required to attend 8 trial visits, with a follow-up call 4 weeks after the last dose.

Reporting group title	Part B: Placebo, 800 mg twice daily

Reporting group description:

Part B consisted of a 4-week baseline period, a 2-week dose-escalation period, a 6-week stable treatment period, and a 12-day taper period. Placebo was taken orally, 800 mg twice daily, for approximately 10 weeks. Participants were required to attend 8 trial visits, with a follow-up call 4 weeks after the last dose.

Primary: Percent Reduction From Baseline In Focal Seizure Frequency In Participants Taking GWP42006 Compared With Placebo During The Treatment Period

End point title	Percent Reduction From Baseline In Focal Seizure Frequency In Participants Taking GWP42006 Compared With Placebo During The Treatment Period[1]

End point description:

This end point reports the evaluation of the efficacy of GWP42006, compared with placebo, as add-on therapy to treat inadequately controlled focal seizures (defined as: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness, and focal seizures evolving to bilateral convulsive seizures). The reported outcome variable was the change from baseline in focal seizure frequency during the treatment period of the trial. Due to non-normality of the seizure data, negative binomial regression analyses were conducted on the sum of the seizure counts during the treatment period; treatment ratios <1 indicate a difference in favor of GWP42006. The intention-to-treat (ITT) analysis set, all participants who were randomized in Part B, was used in the analysis of this end point.

End point type	Primary

End point timeframe:

Baseline, Day 57 (±3)

Notes:

[1] - 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: End point not applicable to Part A as changes in focal seizure frequency were not reported for this part of the trial. This end point provides data for Part B of the trial only.

End point values	Part B: GWP42006, 800 mg twice daily	Part B: Placebo, 800 mg twice daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81[2]	81[3]		
Units: Percent Reduction				
number (confidence interval 95%)	40.5 (31.4 to 48.4)	37.7 (28.2 to 45.9)		

Notes:

[2] - ITT

[3] - ITT

Statistical analyses

Statistical analysis title	Percent Reduction (GWP42006 versus Placebo)
Comparison groups	Part B: GWP42006, 800 mg twice daily v Part B: Placebo, 800 mg twice daily
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.648
Method	Negative Binomial Regression
Parameter estimate	Percent Reduction
Point estimate	4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.7
upper limit	21.9

Notes:

[4] - Treatment Difference

Secondary: Participants Who Experienced Treatment-Related, Treatment-Emergent Adverse Events (TEAEs)

End point title	Participants Who Experienced Treatment-Related, Treatment-Emergent Adverse Events (TEAEs)

End point description:

For both Parts A and B, an AE was defined as any new unfavorable/unintended signs/symptoms (including abnormal laboratory findings), or diagnosis or worsening of a pre-existing condition, which was present following baseline screening and the post-treatment, safety follow-up visit, which may or may not have been considered to be related to the study drug. Any event that was the result of a trial procedure was to be recorded as an AE. A TEAE was defined as an AE with a start date on or after the first dose of study drug. If an AE had a partial start date and it was unclear from the partial date (or the stop date) whether the AE started prior to or post first dose of the study drug, then the AE was considered treatment emergent. An AE was considered treatment-related if the plausibility relationship to the study drug was recorded on the case report form as 'yes'. A summary of serious and other non-serious AEs, regardless of causality, is located in the Adverse Events module.

End point type	Secondary

End point timeframe:

Baseline through Safety Follow-up Visit

End point values	Part A: GWP42006, 400 mg twice daily	Part A: Placebo, 400 mg twice daily	Part B: GWP42006, 800 mg twice daily	Part B: Placebo, 800 mg twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26[5]	6[6]	81[7]	81[8]
Units: Participants	5	2	46	28

Notes:

[5] - Safety Set: All participants who received at least 1 dose of GWP42006.

[6] - Safety Set: All participants who received at least 1 dose of placebo.

[7] - Safety Set: All participants who received at least 1 dose of GWP42006.

[8] - Safety Set: All participants who received at least 1 dose of placebo.

Statistical analyses

No statistical analyses for this end point

Secondary: Participants Considered Treatment Responders

End point title	Participants Considered Treatment Responders[9]

End point description:

The number of participants considered treatment responders in Part B is summarized and reported. Treatment responders were defined as those participants meeting the 4 following response thresholds for percent reduction (compared to baseline) in focal seizure frequency: ≥25%; ≥50%; ≥75%; 100%.

End point type	Secondary

End point timeframe:

Baseline, Day 57 (±3)

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: End point not applicable to Part A as treatment responders were not reported for this part of the trial. This end point provides data for Part B of the trial only.

End point values	Part B: GWP42006, 800 mg twice daily	Part B: Placebo, 800 mg twice daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	81		
Units: Participants				
≥25%	52	53		
≥50%	29	27		
≥75%	11	10		
100%	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Part A: Baseline (up to 2 weeks prior to administration of first dose) to the post-treatment, safety follow-up visit (Week 6).
Part B: Baseline (up to 4 weeks prior to administration of first dose) to the post-treatment, safety follow-up visit (Week 14).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Part A: GWP42006, 400 mg twice daily

Reporting group description:

Part A consisted of a 2-week baseline period and a 2-week treatment period. Participants were required to attend 6 trial visits, with a follow-up call 4 weeks after the last dose of study drug. GWP42006 was taken orally, 400 mg twice daily for 2 weeks, by participants who were categorized into 1 of 3 groups according to their concomitant AED regimen at trial entry. Group 1 included participants who took inducer AEDs (carbamazepine, phenobarbital, primidone, or phenytoin), but did not take inhibitor AEDs (valproic acid). Group 2 included participants who took inhibitor AEDs (valproic acid), but who did not take inducer AEDs (carbamazepine, phenobarbital, primidone, or phenytoin). Group 3 included participants on AEDs that were neither inducers nor inhibitors.

Reporting group title	Part A: Placebo, 400 mg twice daily

Reporting group description:

Part A consisted of a 2-week baseline period and a 2-week treatment period. Participants were required to attend 6 trial visits, with a follow-up call 4 weeks after the last dose of study drug. Placebo was taken orally, 400 mg twice daily for 2 weeks, by participants who were categorized into 1 of 3 groups according to their concomitant AED regimen at trial entry. Group 1 included participants who took inducer AEDs (carbamazepine, phenobarbital, primidone, or phenytoin), but did not take inhibitor AEDs (valproic acid). Group 2 included participants who took inhibitor AEDs (valproic acid), but who did not take inducer AEDs (carbamazepine, phenobarbital, primidone, or phenytoin). Group 3 included participants on AEDs that were neither inducers nor inhibitors.

Reporting group title	Part B: GWP42006, 800 mg twice daily

Reporting group description:

Part B consisted of a 4-week baseline period, a 2-week dose-escalation period, a 6-week stable treatment period, and a 12-day taper period. GWP42006 was taken orally, 800 mg twice daily, for approximately 10 weeks. Participants were required to attend 8 trial visits, with a follow-up call 4 weeks after the last dose.

Reporting group title	Part B: Placebo, 800 mg twice daily

Reporting group description:

Part B consisted of a 4-week baseline period, a 2-week dose-escalation period, a 6-week stable treatment period, and a 12-day taper period. Placebo was taken orally, 800 mg twice daily, for approximately 10 weeks. Participants were required to attend 8 trial visits, with a follow-up call 4 weeks after the last dose.

Serious adverse events	Part A: GWP42006, 400 mg twice daily	Part A: Placebo, 400 mg twice daily	Part B: GWP42006, 800 mg twice daily
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	3 / 81 (3.70%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Status epilepticus			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	0 / 81 (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			
Diarrhoea			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part B: Placebo, 800 mg twice daily		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 81 (1.23%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Status epilepticus			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part A: GWP42006, 400 mg twice daily	Part A: Placebo, 400 mg twice daily	Part B: GWP42006, 800 mg twice daily
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 26 (11.54%)	4 / 6 (66.67%)	39 / 81 (48.15%)
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 26 (0.00%)	1 / 6 (16.67%)	2 / 81 (2.47%)
occurrences (all)	0	1	2
Dizziness			
subjects affected / exposed	1 / 26 (3.85%)	0 / 6 (0.00%)	5 / 81 (6.17%)
occurrences (all)	1	0	5
Headache			
subjects affected / exposed	0 / 26 (0.00%)	1 / 6 (16.67%)	7 / 81 (8.64%)
occurrences (all)	0	1	9
Memory impairment			
subjects affected / exposed	0 / 26 (0.00%)	1 / 6 (16.67%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Neuralgia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 6 (16.67%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	12 / 81 (14.81%)
occurrences (all)	0	0	14
Tremor			
subjects affected / exposed	0 / 26 (0.00%)	1 / 6 (16.67%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 26 (0.00%)	1 / 6 (16.67%)	2 / 81 (2.47%)
occurrences (all)	0	1	2
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	5 / 81 (6.17%)
occurrences (all)	0	0	5
Diarrhoea			
subjects affected / exposed	2 / 26 (7.69%)	0 / 6 (0.00%)	20 / 81 (24.69%)
occurrences (all)	2	0	23

Nausea			
subjects affected / exposed	1 / 26 (3.85%)	1 / 6 (16.67%)	8 / 81 (9.88%)
occurrences (all)	2	1	8
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 6 (16.67%)	1 / 81 (1.23%)
occurrences (all)	0	1	1
Affect lability			
subjects affected / exposed	0 / 26 (0.00%)	1 / 6 (16.67%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Mood altered			
subjects affected / exposed	0 / 26 (0.00%)	1 / 6 (16.67%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Muscle contracture			
subjects affected / exposed	0 / 26 (0.00%)	1 / 6 (16.67%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	2 / 81 (2.47%)
occurrences (all)	0	0	2

Non-serious adverse events	Part B: Placebo, 800 mg twice daily		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 81 (28.40%)		
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	4		
Headache			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	25		
Memory impairment			

subjects affected / exposed occurrences (all) Neuralgia subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0 0 / 81 (0.00%) 0 2 / 81 (2.47%) 2 1 / 81 (1.23%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	 1 / 81 (1.23%) 1		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 1 / 81 (1.23%) 2 6 / 81 (7.41%) 7 8 / 81 (9.88%) 9		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Affect lability subjects affected / exposed occurrences (all) Mood altered subjects affected / exposed occurrences (all)	 3 / 81 (3.70%) 3 0 / 81 (0.00%) 0 0 / 81 (0.00%) 0		
Musculoskeletal and connective tissue disorders			

Muscle contracture subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	6 / 81 (7.41%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2016	Amendment 13: Additional pharmacokinetics sample and metabolite analysis.
11 May 2016	Amendment 14 and Amendment 15: Additional pharmacokinetics sample and metabolite analysis.
25 October 2016	Amendment 16, Amendment 17, and Amendment 18: Increase power to 90% and Part B sample size to 140.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported