



Clinical trial results:

A Phase 2, Double-blind, Randomized, Placebo-controlled, Pharmacokinetic Trial in Two Parallel Groups to Investigate Possible Drug-drug Interactions Between Stiripentol or Valproate and GWP42003-P in Patients with Epilepsy

Summary

EudraCT number	2015-002939-18
Trial protocol	ES SE NL PL
Global end of trial date	27 May 2019

Results information

Result version number	v1 (current)
This version publication date	05 April 2020
First version publication date	05 April 2020

Trial information

Trial identification

Sponsor protocol code	GWEP1447
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Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 May 2019
Global end of trial reached?	Yes
Global end of trial date	27 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study investigates possible drug-drug interactions between stiripentol or valproate and GWP42003-P in patients with epilepsy

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and subsequent amendments. This trial was also designed to comply with ICH E6 Guideline for good clinical practice (EMA/CHMP/ICH/135/1995) and the European Clinical Trial Directive 2001/20/EC. The International Council for Harmonisation adopted guidelines and other relevant international guidelines, recommendations and requirements were taken into account as comprehensively as possible, as long as they did not violate Spanish, Swedish or Dutch law.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Sweden: 19
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	0
Adolescents (12-17 years)	1

Adults (18-64 years)	34
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were screened to assess their eligibility to enter the trial within 15 days prior to the first dose administration.

Pre-assignment period milestones

Number of subjects started	35
Number of subjects completed	34

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not meet inclusion/exclusion criteria;: 1
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Period 1

Period 1 title	Double Blind (DB)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
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Arm title	STP + GWP42003-P
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Arm description:

On Day 2, subjects received an oral administration of GWP42003-P twice daily (morning and evening; immediately after the subject's stiripentol [STP] dose), commencing with up-titration of 100 milligrams per milliliter (mg/mL) GWP42003-P to a maintenance dose of 20 milligrams per kilogram per day (mg/kg/day) over 10 days (Days 2 to 11). After titration with GWP42003-P, subjects continued to take the maintenance dose of GWP42003-P for 14 days (Days 12 to 25). On Day 27, subjects either entered a tapering period (10% per day over 10 days) or, if the subject elected to participate in the open-label extension study, they entered a 10-day period of simultaneous tapering (of GWP42003-P) and titration (of GWP42003-P) in order to maintain blinding.

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

Dosage and administration details:

Oral liquid formulation that is clear and colorless to yellow in appearance (100 milligrams per milliliter [mg/mL]), in sesame oil with anhydrous ethanol, added sweetener (sucralose) and strawberry flavoring. The oral liquid formulation was administered with a syringe.

Arm title	STP + Placebo
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Arm description:

On Day 2, subjects received an oral administration of matching placebo twice daily (morning and evening; immediately after the subject's STP dose), commencing with up-titration of 100 mg/mL placebo to a maintenance dose of 20 mg/kg/day over 10 days (Days 2 to 11). After titration with placebo, subjects continued to take the maintenance dose of placebo for 14 days (Days 12 to 25). On Day 27, subjects either entered a tapering period (10% per day over 10 days) or, if the subject elected to participate in the open-label extension study, they entered a 10-day period of simultaneous tapering (of placebo) and titration (of placebo) in order to maintain blinding.

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:

Volume of GW placebo solution equivalent to the planned GWP42003-P dose.

Arm title	VPA + GWP42003-P
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Arm description:

On Day 2, subjects received an oral administration of GWP42003-P twice daily (morning and evening; immediately after the subject's Valproate [VPA] dose), commencing with up-titration of 100 mg/mL GWP42003-P to a maintenance dose of 20 mg/kg/day over 10 days (Days 2 to 11). After titration with GWP42003-P, subjects continued to take the maintenance dose of GWP42003-P for 14 days (Days 12 to 25). On Day 27, subjects either entered a tapering period (10% per day over 10 days) or, if the subject elected to participate in the open-label extension study, they entered a 10-day period of simultaneous tapering (of GWP42003-P) and titration (of GWP42003-P) in order to maintain blinding.

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

Dosage and administration details:

Oral liquid formulation that is clear and colorless to yellow in appearance (100 milligrams per milliliter [mg/mL]), in sesame oil with anhydrous ethanol, added sweetener (sucralose) and strawberry flavoring. The oral liquid formulation was administered with a syringe.

Arm title	VPA + Placebo
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Arm description:

On Day 2, subjects received an oral administration of matching placebo twice daily (morning and evening; immediately after the subject's VPA dose), commencing with up-titration of 100 mg/mL placebo to a maintenance dose of 20 mg/kg/day over 10 days (Days 2 to 11). After titration with placebo, subjects continued to take the maintenance dose of placebo for 14 days (Days 12 to 25). On Day 27, subjects either entered a tapering period (10% per day over 10 days) or, if the subject elected to participate in the open-label extension study, they entered a 10-day period of simultaneous tapering (of placebo) and titration (of placebo) in order to maintain blinding.

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:

Volume of GW placebo solution equivalent to the planned GWP42003-P dose.

Number of subjects in period 1^[1]	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P
Started	12	2	16
Completed	10	2	14
Not completed	2	0	2
Adverse event, non-fatal	1	-	-

Withdrawn Consent	-	-	2
Met Withdraw Criteria	1	-	-

Number of subjects in period 1 ^[1]	VPA + Placebo
Started	4
Completed	4
Not completed	0
Adverse event, non-fatal	-
Withdrawn Consent	-
Met Withdraw Criteria	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One subject withdrew before receiving the first dose of investigational medicinal product. Baseline data are not reported for this subject.

Period 2

Period 2 title	Open Label Extension (OLE)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	STP/VPA + GWP42003-P
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Arm description:

Subjects completing the DB period were invited to participate in the OLE period. Subjects taking GWP42003-P during the DB period maintained their dose throughout the transition from the DB period into the OLE period. Subjects who received placebo during the DB period titrated 10% over 10 days to reach their maximum tolerable dose not to exceed 20 mg/kg/day in the OLE period. All subjects continued their STP or VPA as per physician's orders.

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

Dosage and administration details:

Oral liquid formulation that is clear and colorless to yellow in appearance (100 milligrams per milliliter [mg/mL]), in sesame oil with anhydrous ethanol, added sweetener (sucralose) and strawberry flavoring. The oral liquid formulation was administered with a syringe.

Number of subjects in period 2	STP/VPA + GWP42003-P
Started	30
Completed	13
Not completed	17
Subject withdrew consent	5
Adverse event, non-fatal	9

Not specified	2
Subject withdrawn by Investigator	1

Baseline characteristics

Reporting groups

Reporting group title	STP + GWP42003-P
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Reporting group description:

On Day 2, subjects received an oral administration of GWP42003-P twice daily (morning and evening; immediately after the subject's stiripentol [STP] dose), commencing with up-titration of 100 milligrams per milliliter (mg/mL) GWP42003-P to a maintenance dose of 20 milligrams per kilogram per day (mg/kg/day) over 10 days (Days 2 to 11). After titration with GWP42003-P, subjects continued to take the maintenance dose of GWP42003-P for 14 days (Days 12 to 25). On Day 27, subjects either entered a tapering period (10% per day over 10 days) or, if the subject elected to participate in the open-label extension study, they entered a 10-day period of simultaneous tapering (of GWP42003-P) and titration (of GWP42003-P) in order to maintain blinding.

Reporting group title	STP + Placebo
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Reporting group description:

On Day 2, subjects received an oral administration of matching placebo twice daily (morning and evening; immediately after the subject's STP dose), commencing with up-titration of 100 mg/mL placebo to a maintenance dose of 20 mg/kg/day over 10 days (Days 2 to 11). After titration with placebo, subjects continued to take the maintenance dose of placebo for 14 days (Days 12 to 25). On Day 27, subjects either entered a tapering period (10% per day over 10 days) or, if the subject elected to participate in the open-label extension study, they entered a 10-day period of simultaneous tapering (of placebo) and titration (of placebo) in order to maintain blinding.

Reporting group title	VPA + GWP42003-P
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Reporting group description:

On Day 2, subjects received an oral administration of GWP42003-P twice daily (morning and evening; immediately after the subject's Valproate [VPA] dose), commencing with up-titration of 100 mg/mL GWP42003-P to a maintenance dose of 20 mg/kg/day over 10 days (Days 2 to 11). After titration with GWP42003-P, subjects continued to take the maintenance dose of GWP42003-P for 14 days (Days 12 to 25). On Day 27, subjects either entered a tapering period (10% per day over 10 days) or, if the subject elected to participate in the open-label extension study, they entered a 10-day period of simultaneous tapering (of GWP42003-P) and titration (of GWP42003-P) in order to maintain blinding.

Reporting group title	VPA + Placebo
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Reporting group description:

On Day 2, subjects received an oral administration of matching placebo twice daily (morning and evening; immediately after the subject's VPA dose), commencing with up-titration of 100 mg/mL placebo to a maintenance dose of 20 mg/kg/day over 10 days (Days 2 to 11). After titration with placebo, subjects continued to take the maintenance dose of placebo for 14 days (Days 12 to 25). On Day 27, subjects either entered a tapering period (10% per day over 10 days) or, if the subject elected to participate in the open-label extension study, they entered a 10-day period of simultaneous tapering (of placebo) and titration (of placebo) in order to maintain blinding.

Reporting group values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P
Number of subjects	12	2	16
Age categorical			
Units: Subjects			
<=18 years	0	0	1
Between 18 and 65 years	12	2	15
>=65 years	0	0	0
Age continuous			
Units: years			
arithmetic mean	31.34	20.95	29.14
standard deviation	± 11.09	± 3.04	± 11.40
Gender categorical			
Units: Subjects			
Female	5	0	6
Male	7	2	10

Reporting group values	VPA + Placebo	Total	
Number of subjects	4	34	
Age categorical Units: Subjects			
≤18 years	0	1	
Between 18 and 65 years	4	33	
≥65 years	0	0	
Age continuous Units: years			
arithmetic mean	29.80		
standard deviation	± 6.60	-	
Gender categorical Units: Subjects			
Female	1	12	
Male	3	22	

End points

End points reporting groups

Reporting group title	STP + GWP42003-P
Reporting group description: On Day 2, subjects received an oral administration of GWP42003-P twice daily (morning and evening; immediately after the subject's stiripentol [STP] dose), commencing with up-titration of 100 milligrams per milliliter (mg/mL) GWP42003-P to a maintenance dose of 20 milligrams per kilogram per day (mg/kg/day) over 10 days (Days 2 to 11). After titration with GWP42003-P, subjects continued to take the maintenance dose of GWP42003-P for 14 days (Days 12 to 25). On Day 27, subjects either entered a tapering period (10% per day over 10 days) or, if the subject elected to participate in the open-label extension study, they entered a 10-day period of simultaneous tapering (of GWP42003-P) and titration (of GWP42003-P) in order to maintain blinding.	
Reporting group title	STP + Placebo
Reporting group description: On Day 2, subjects received an oral administration of matching placebo twice daily (morning and evening; immediately after the subject's STP dose), commencing with up-titration of 100 mg/mL placebo to a maintenance dose of 20 mg/kg/day over 10 days (Days 2 to 11). After titration with placebo, subjects continued to take the maintenance dose of placebo for 14 days (Days 12 to 25). On Day 27, subjects either entered a tapering period (10% per day over 10 days) or, if the subject elected to participate in the open-label extension study, they entered a 10-day period of simultaneous tapering (of placebo) and titration (of placebo) in order to maintain blinding.	
Reporting group title	VPA + GWP42003-P
Reporting group description: On Day 2, subjects received an oral administration of GWP42003-P twice daily (morning and evening; immediately after the subject's Valproate [VPA] dose), commencing with up-titration of 100 mg/mL GWP42003-P to a maintenance dose of 20 mg/kg/day over 10 days (Days 2 to 11). After titration with GWP42003-P, subjects continued to take the maintenance dose of GWP42003-P for 14 days (Days 12 to 25). On Day 27, subjects either entered a tapering period (10% per day over 10 days) or, if the subject elected to participate in the open-label extension study, they entered a 10-day period of simultaneous tapering (of GWP42003-P) and titration (of GWP42003-P) in order to maintain blinding.	
Reporting group title	VPA + Placebo
Reporting group description: On Day 2, subjects received an oral administration of matching placebo twice daily (morning and evening; immediately after the subject's VPA dose), commencing with up-titration of 100 mg/mL placebo to a maintenance dose of 20 mg/kg/day over 10 days (Days 2 to 11). After titration with placebo, subjects continued to take the maintenance dose of placebo for 14 days (Days 12 to 25). On Day 27, subjects either entered a tapering period (10% per day over 10 days) or, if the subject elected to participate in the open-label extension study, they entered a 10-day period of simultaneous tapering (of placebo) and titration (of placebo) in order to maintain blinding.	
Reporting group title	STP/VPA + GWP42003-P
Reporting group description: Subjects completing the DB period were invited to participate in the OLE period. Subjects taking GWP42003-P during the DB period maintained their dose throughout the transition from the DB period into the OLE period. Subjects who received placebo during the DB period titrated 10% over 10 days to reach their maximum tolerable dose not to exceed 20 mg/kg/day in the OLE period. All subjects continued their STP or VPA as per physician's orders.	

Primary: Double Blind: Dose Normalized (DN) Cmax of STP and VPA

End point title	Double Blind: Dose Normalized (DN) Cmax of STP and VPA ^[1]
End point description: Cmax is the maximum measured plasma concentration. Blood samples were collected for pharmacokinetic (PK) analysis predose, 15 and 30 minutes, then 1, 1.5, 2, 4, 6, and 12 hours postdose. 999=No analysis was conducted for this treatment arm at this time point. n=number of subjects with evaluable data. The PK analysis set includes all subjects enrolled in the trial who received at least 1 dose of GWP42003-P or placebo and who provided some on-treatment data.	
End point type	Primary

End point timeframe:

Day 1 and Day 26

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 analysis (for example, a p-value) was not performed for the PK endpoints. Descriptive statistics are included (geometric mean and % CV).

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[2]	2 ^[3]	12 ^[4]	3 ^[5]
Units: nanograms per milliliter per milligram				
geometric mean (geometric coefficient of variation)				
STP Day 1 n=11,2,0,0	7.6 (± 80.0)	7.74 (± 16.3)	999 (± 999)	999 (± 999)
STP Day 26 n=9,2,0,0	10.7 (± 59.4)	7.65 (± 18.4)	999 (± 999)	999 (± 999)
VPA Day 1 n=0,0,12,3	999 (± 999)	999 (± 999)	173 (± 54.7)	161 (± 54.1)
VPA Day 26 n=0,0,10,3	999 (± 999)	999 (± 999)	143 (± 60.6)	168 (± 46.6)

Notes:

[2] - PK Analysis Set

[3] - PK Analysis Set

[4] - PK Analysis Set

[5] - PK Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Double Blind: DN Cmax of CBD

End point title	Double Blind: DN Cmax of CBD ^[6] ^[7]
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End point description:

Cmax is the maximum measured plasma concentration. Blood samples were collected for PK analysis predose, 15 and 30 minutes, then 1, 1.5, 2, 4, 6, and 12 hours postdose.

The PK analysis set includes all subjects enrolled in the trial who received at least 1 dose of GWP42003-P or placebo and who provided some on-treatment data.

End point type	Primary
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End point timeframe:

Day 26

Notes:

[6] - 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 analysis (for example, a p-value) was not performed for the PK endpoints. Descriptive statistics are included (geometric mean and % CV).

[7] - 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 analysis (for example, a p-value) was not performed for the PK endpoints. Descriptive statistics are included (geometric mean and % CV).

End point values	STP + GWP42003-P	VPA + GWP42003-P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[8]	10 ^[9]		
Units: ng/mL/[mg/kg]				
geometric mean (geometric coefficient of variation)	35.1 (± 64.4)	25.4 (± 54.1)		

Notes:

[8] - PK Analysis Set. Only subjects with available data were analyzed.

[9] - PK Analysis Set. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Double Blind: tmax of STP, VPA and CBD^[10]

End point title	Double Blind: tmax of STP, VPA and CBD ^[10]
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End point description:

tmax is the time to the maximum measured plasma concentration. Blood samples were collected for PK analysis predose, 15 and 30 minutes, then 1, 1.5, 2, 4, 6, and 12 hours postdose.

999=No analysis was conducted for this treatment arm at this time point.

n=number of subjects with evaluable data.

The PK analysis set includes all subjects enrolled in the trial who received at least 1 dose of GWP42003-P or placebo and who provided some on-treatment data.

End point type	Primary
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End point timeframe:

Day 1 and Day 26

Notes:

[10] - 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 analysis (for example, a p-value) was not performed for the PK endpoints. Descriptive statistics are included (geometric mean and full range).

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[11]	2 ^[12]	12 ^[13]	3 ^[14]
Units: hours (h)				
geometric mean (full range (min-max))				
STP Day 1 n=11,2,0,0	1.53 (0.25 to 6.08)	3.94 (2.00 to 5.88)	999 (999 to 999)	999 (999 to 999)
STP Day 26 n=9,2,0,0	2.07 (1.42 to 6.03)	1.70 (1.40 to 2.00)	999 (999 to 999)	999 (999 to 999)
VPA Day 1 n=0,0,12,3	999 (999 to 999)	999 (999 to 999)	3.03 (0.00 to 6.17)	3.92 (1.50 to 4.00)
VPA Day 26 n=0,0,10,3	999 (999 to 999)	999 (999 to 999)	1.76 (0.00 to 12.00)	4.00 (0.00 to 6.00)
CBD Day 26 n=10,0,10,0	4.05 (0.00 to 6.02)	999 (999 to 999)	2.33 (1.00 to 6.00)	999 (999 to 999)

Notes:

[11] - PK Analysis Set

[12] - PK Analysis Set

[13] - PK Analysis Set

[14] - PK Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Double Blind: DN AUCtau of STP and VPA

End point title	Double Blind: DN AUCtau of STP and VPA ^[15]
End point description:	
AUCtau is the area under the concentration-time curve over the dosing interval. Blood samples were collected for PK analysis predose, 15 and 30 minutes, then 1, 1.5, 2, 4, 6, and 12 hours postdose. 999=No analysis was conducted for this treatment arm at this time point. n=number of subjects with evaluable data. The PK analysis set includes all subjects enrolled in the trial who received at least 1 dose of GWP42003-P or placebo and who provided some on-treatment data.	
End point type	Primary
End point timeframe:	
Day 1 and Day 26	

Notes:

[15] - 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 analysis (for example, a p-value) was not performed for the PK endpoints. Descriptive statistics are included (geometric mean and % CV).

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[16]	2 ^[17]	12 ^[18]	3 ^[19]
Units: ngxh/mL/mg				
geometric mean (geometric coefficient of variation)				
STP Day 1 n=11,2,0,0	52.3 (± 108.5)	49.7 (± 22.0)	999 (± 999)	999 (± 999)
STP Day 26 n=9,2,0,0	80.7 (± 66.8)	51.8 (± 41.3)	999 (± 999)	999 (± 999)
VPA Day 1 n=0,0,12,3	999 (± 999)	999 (± 999)	1710 (± 64.3)	1620 (± 63.2)
VPA Day 26 n=0,0,10,3	999 (± 999)	999 (± 999)	1350 (± 62.2)	1540 (± 51.4)

Notes:

[16] - PK Analysis Set

[17] - PK Analysis Set

[18] - PK Analysis Set

[19] - PK Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Double Blind: DN AUCtau of CBD

End point title	Double Blind: DN AUCtau of CBD ^{[20][21]}
End point description:	
AUCtau is the area under the concentration-time curve over the dosing interval. Blood samples were collected for PK analysis predose, 15 and 30 minutes, then 1, 1.5, 2, 4, 6, and 12 hours postdose. The PK analysis set includes all subjects enrolled in the trial who received at least 1 dose of GWP42003-P or placebo and who provided some on-treatment data.	
End point type	Primary
End point timeframe:	
Day 26	

Notes:

[20] - 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 analysis (for example, a p-value) was not performed for the PK endpoints. Descriptive statistics are included (geometric mean and % CV).

[21] - 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 analysis (for example, a p-value) was not performed for the PK endpoints. Descriptive statistics are included (geometric mean and % CV).

End point values	STP + GWP42003-P	VPA + GWP42003-P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[22]	10 ^[23]		
Units: ngxh/mL/[mg/kg]				
geometric mean (geometric coefficient of variation)	203 (± 48.1)	145 (± 52.3)		

Notes:

[22] - PK Analysis Set. Only subjects with available data were analyzed.

[23] - PK Analysis Set. Only subjects with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: OLE: Number of subjects with adverse events (AE)

End point title	OLE: Number of subjects with adverse events (AE) ^[24]
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End point description:

An AE is 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 screening (Visit 1) and at any point up to the post treatment, safety follow-up visit (Visit 6 if patients did not enter the OLE or Visit 13 if they completed the OLE or 28 [± 3] days following the last dose of IMP), which may or may not have been considered to be related to the IMP. Results are categorized by system organ class and then by all-causality (any and all AEs, regardless of relation to IMP [investigational medicinal product]) and treatment-related (an AE marked as possibly attributed to IMP).

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Primary
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End point timeframe:

Day 40 to Day 418

Notes:

[24] - 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 analysis (for example, a p-value) was not performed for this endpoint.

End point values	STP/VPA + GWP42003-P			
Subject group type	Reporting group			
Number of subjects analysed	30 ^[25]			
Units: subjects				
Gastrointestinal Disorders, All-causality	19			
Gastrointestinal Disorders, Treatment-related	16			
Nervous System Disorders, All-causality	10			
Nervous System Disorders, Treatment-related	5			
Investigations, All-causality	9			
Investigations, Treatment-related	8			
Infections, All-causality	6			
Infections, Treatment-related	1			
Psychiatric Disorders, All-causality	6			
Psychiatric Disorders, Treatment-related	5			
General Disorders, All-causality	5			
General Disorders, Treatment-related	4			
Skin Disorders, All-causality	4			
Skin Disorders, Treatment-related	3			

Musculoskeletal Disorders, All-causality	3			
Musculoskeletal Disorders, Treatment-related	1			

Notes:

[25] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: OLE: Number of subjects with shifts from normal in hematology laboratory values

End point title	OLE: Number of subjects with shifts from normal in hematology laboratory values ^[26]
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End point description:

Results are categorized by the number of subjects with a shift from normal to low (N2L) or normal to high (N2H) at Visit 5 (V5, Day 40), Visit 6 (V6, Day 54), Visit 7 (V7, Day 82), Visit 8 (V8, Day 110), Visit 9 (V9, Day 194), Visit 10 (V10, Day 278), Visit 11 (V11, Day 362) and Visit 12 (V12, Day 372). The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Primary
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End point timeframe:

Day 40 to Day 372

Notes:

[26] - 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 analysis (for example, a p-value) was not performed for this endpoint.

End point values	STP/VPA + GWP42003-P			
Subject group type	Reporting group			
Number of subjects analysed	30 ^[27]			
Units: subjects				
V5, N2L, Hematocrit	6			
V5, N2L, Lymphocytes	1			
V5, N2L, Neutrophils	2			
V5, N2L, Red Blood Cell Count (blood)	2			
V5, N2H, Absolute Monocyte Count	3			
V5, N2H, Lymphocytes	3			
V5, N2H, Monocytes	2			
V5, N2H, Neutrophils	1			
V5, N2H, White Blood Cells Count with Differential	1			
V6, N2L, Absolute Neutrophil Count	1			
V6, N2L, Hematocrit	4			
V6, N2L, Hemoglobin	1			
V6, N2L, Lymphocytes	1			
V6, N2L, Neutrophils	2			
V6, N2L, Platelets	1			
V6, N2L, Red Blood Cell Count (blood)	5			
V6, N2L, White Blood Cell Count with Differential	1			
V6, N2H, Absolute Eosinophil Count	1			
V6, N2H, Absolute Monocyte Count	3			

V6, N2H, Eosinophils	3			
V6, N2H, Lymphocytes	4			
V6, N2H, Mean Cell Volume	1			
V6, N2H, Monocytes	2			
V6, N2H, Neutrophils	1			
V7, N2L, Hemtocrit	4			
V7, N2L, Neutrophils	3			
V7, N2L, Platelets	1			
V7, N2L, Red Blood Cell Count (blood)	3			
V7, N2L, White Blood Cell Count with Differential	3			
V7, N2H, Eosinophils	3			
V7, N2H, Lymphoblasts	1			
V7, N2H, Lymphocytes	3			
V7, N2H, Mean Cell Volume	1			
V7, N2H, Monocytes	2			
V7, N2H, Neutrophils	1			
V8, N2L, Absolute Neutrophil Count	1			
V8, N2L, Hematocrit	4			
V8, N2L, Hemoglobin	2			
V8, N2L, Lymphoblasts	1			
V8, N2L, Lymphocytes	4			
V8, N2L, Neutrophils	1			
V8, N2L, Platelets	1			
V8, N2L, Red Blood Cell Count (blood)	3			
V8, N2L, White Blood Cell Count with Differential	1			
V8, N2H, Absolute Monocyte Count	2			
V8, N2H, Eosinophils	2			
V8, N2H, Lymphocytes	3			
V8, N2H, Monocytes	3			
V8, N2H, Neutrophils	1			
V9, N2L, Hematocrit	1			
V9, N2L, Lymphocytes	5			
V9, N2L, Red Blood Cell Count (blood)	4			
V9, N2L, White Blood Cell Count with Differential	1			
V9, N2H, Absolute Monocyte Count	2			
V9, N2H, Absolute Neutrophil Count	1			
V9, N2H, Lymphocytes	1			
V9, N2H, Mean Cell Volume	1			
V9, N2H, Monocytes	1			
V9, N2H, Neutrophils	3			
V9, N2H, White Blood Cell Count with Differential	1			
V10, N2L, Absolute Neutrophil Count	1			
V10, N2L, Lymphoblasts	1			
V10, N2L, Lymphocytes	2			
V10, N2L, Neutrophils	2			
V10, N2L, Platelets	1			
V10, N2L, Red Blood Cell Count (blood)	2			
V10, N2L, White Blood Cell Count with Differential	1			

V10, N2H, Lymphocytes	1			
V10, N2H, Monocytes	1			
V10, N2H, Neutrophils	1			
V11, N2L, Absolute Neutrophil Count	2			
V11, N2L, Hematocrit	5			
V11, N2L, Hemoglobin	1			
V11, N2L, Lymphocytes	1			
V11, N2L, Neutrophils	3			
V11, N2L, Platelets	1			
V11, N2L, Red Blood Cell Count (blood)	4			
V11, N2L, White Blood Cell Count with Differential	2			
V11, N2H, Absolute Eosinophil Count	1			
V11, N2H, Eosinophils	2			
V11, N2H, Lymphoblasts	1			
V11, N2H, Lymphocytes	2			
V11, N2H, Mean Cell Volume	1			
V11, N2H, Monocytes	1			
V11, N2H, Neutrophils	1			
V12, N2L, Absolute Neutrophil Count	1			
V12, N2L, Hematocrit	4			
V12, N2L, Lymphocytes	1			
V12, N2L, Mean Cell Volume	1			
V12, N2L, Neutrophils	1			
V12, N2L, Red Blood Cell Count (blood)	1			
V12, N2L, White Blood Cell Count with Differential	1			
V12, N2H, Lymphocytes	3			
V12, N2H, Mean Cell Volume	1			
V12, N2H, Monocytes	2			

Notes:

[27] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: OLE: Number of subjects with shifts from normal in biochemistry laboratory values

End point title	OLE: Number of subjects with shifts from normal in biochemistry laboratory values ^[28]
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End point description:

Results are categorized by the number of subjects with a shift from normal to low (N2L) or normal to high (N2H) at Visit 5 (V5, Day 40), Visit 6 (V6, Day 54), Visit 7 (V7, Day 82), Visit 8 (V8, Day 110), Visit 9 (V9, Day 194), Visit 10 (V10, Day 278), Visit 11 (V11, Day 362) and Visit 12 (V12, Day 372).

HDL=high-density lipoprotein.

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Primary
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End point timeframe:

Day 40 to Day 372

Notes:

[28] - 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 analysis (for example, a p-value) was not performed for this

endpoint.

End point values	STP/VPA + GWP42003-P			
Subject group type	Reporting group			
Number of subjects analysed	30 ^[29]			
Units: subjects				
V5, N2L, Alkaline Phosphatase	1			
V5, N2L, HDL-Cholesterol	1			
V5, N2L, Sodium	2			
V5, N2L, Total Bilirubin (blood)	1			
V5, N2L, Urea Nitrogen	1			
V5, N2H, Alanine Aminotransferase	8			
V5, N2H, Alkaline Phosphatase	1			
V5, N2H, Aspartate Aminotransferase	6			
V5, N2H, Gamma-glutamyl transferase	4			
V5, N2H, Glucose (blood)	1			
V5, N2H, HDL-Cholesterol	2			
V5, N2H, Prolactin	1			
V5, N2H, Sodium	1			
V5, N2H, Total Bilirubin (blood)	1			
V5, N2H, Triglycerides	3			
V6, N2L, Alkaline Phosphatase	3			
V6, N2L, Aspartate Aminotransferase	1			
V6, N2L, Calcium	2			
V6, N2L, HDL-Cholesterol	1			
V6, N2L, Sodium	1			
V6, N2L, Total Bilirubin (blood)	4			
V6, N2L, Total Protein (blood)	2			
V6, N2H, Alanine Aminotransferase	9			
V6, N2H, Alkaline Phosphatase	1			
V6, N2H, Aspartate Aminotransferase	7			
V6, N2H, Gamma-glutamyl Transferase	4			
V6, N2H, Glucose (blood)	1			
V6, N2H, HDL-Cholesterol	1			
V6, N2H, Sodium	1			
V6, N2H, Triglycerides	3			
V7, N2L, Alkaline Phosphatase	4			
V7, N2L, Sodium	1			
V7, N2L, Total Bilirubin (blood)	3			
V7, N2L, Total Protein (blood)	4			
V7, N2L, Urea Nitrogen	2			
V7, N2H, Alanine Aminotransferase	5			
V7, N2H, Aspartate Aminotransferase	1			
V7, N2H, Gamma-glutamyl Transferase	2			
V7, N2H, Glucose (blood)	1			
V7, N2H, HDL-Cholesterol	2			
V7, N2H, Sodium	1			
V7, N2H, Triglycerides	1			
V8, N2L, Alkaline Phosphatase	5			

V8, N2L, Aspartate Aminotransferase	1			
V8, N2L, Calcium	1			
V8, N2L, Sodium	2			
V8, N2L, Total Bilirubin (blood)	2			
V8, N2L, Total Protein (blood)	2			
V8, N2H, Alanine Aminotransferase	3			
V8, N2H, Aspartate Aminotransferase	2			
V8, N2H, Gamma-glutamyl Transferase	1			
V8, N2H, Glucose (blood)	1			
V8, N2H, HDL-Cholesterol	1			
V8, N2H, Triglycerides	1			
V8, N2H, Urea Nitrogen	2			
V9, N2L, Alkaline Phosphatase	1			
V9, N2L, Calcium	1			
V9, N2L, HDL-Cholesterol	1			
V9, N2L, Total Bilirubin (blood)	3			
V9, N2L, Total Protein (blood)	1			
V9, N2H, Alanine Aminotransferase	3			
V9, N2H, Aspartate Aminotransferase	1			
V9, N2H, Gamma-glutamyl Transferase	1			
V9, N2H, HDL-Cholesterol	1			
V9, N2H, Prolactin	1			
V9, N2H, Total Bilirubin (blood)	1			
V9, N2H, Triglycerides	2			
V10, N2L, Alkaline Phosphatase	1			
V10, N2L, Sodium	1			
V10, N2L, Total Bilirubin (blood)	1			
V10, N2L, Total Protein (blood)	1			
V10, N2H, Alanine Aminotransferase	1			
V10, N2H, Aspartate Aminotransferase	1			
V10, N2H, Gamma-glutamyl Transferase	1			
V10, N2H, Total Bilirubin (blood)	1			
V10, N2H, Triglycerides	3			
V11, N2L, Alkaline Phosphatase	4			
V11, N2L, Aspartate Phosphatase	1			
V11, N2L, Calcium	3			
V11, N2L, Creatine (Jaffe)	1			
V11, N2L, HDL-Cholesterol	1			
V11, N2L, Sodium	1			
V11, N2L, Total Bilirubin (blood)	4			
V11, N2L, Total Protein (blood)	3			
V11, N2L, Urea Nitrogen	1			
V11, N2H, Alanine Aminotransferase	5			
V11, N2H, Aspartate Aminotransferase	3			
V11, N2H, Gamma-glutamyl Transferase	5			
V11, N2H, HDL-Cholesterol	3			
V11, N2H, Potassium	1			
V11, N2H, Prolactin	2			
V11, N2H, Triglycerides	2			
V11, N2H, Urea Nitrogen	1			
V12, N2L, Alkaline Phosphatase	1			
V12, N2L, Aspartate Aminotransferase	1			

V12, N2L, Calcium	2			
V12, N2L, Total Bilirubin (blood)	3			
V12, N2L, Total Protein (blood)	1			
V12, N2L, Urea Nitrogen	1			
V12, N2H, Alanine Aminotransferase	3			
V12, N2H, Aspartate Aminotransferase	3			
V12, N2H, Gamma-glutamyl Transferase	1			

Notes:

[29] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: OLE: Number of subjects with shifts from normal in urinalysis laboratory values

End point title	OLE: Number of subjects with shifts from normal in urinalysis laboratory values ^[30]
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End point description:

Results are categorized by the number of subjects with a shift from normal to low (N2L) or normal to high (N2H).

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Primary
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End point timeframe:

Day 40 to Day 372

Notes:

[30] - 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 analysis (for example, a p-value) was not performed for this endpoint.

End point values	STP/VPA + GWP42003-P			
Subject group type	Reporting group			
Number of subjects analysed	30 ^[31]			
Units: subjects				
N2L	0			
N2H	0			

Notes:

[31] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: OLE: Number of subjects with physical examination findings indicative of an adverse event

End point title	OLE: Number of subjects with physical examination findings indicative of an adverse event ^[32]
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End point description:

Subjects were assessed for adverse events during physical examinations at every visit.

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Primary
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End point timeframe:

Day 40 to Day 372

Notes:

[32] - 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 analysis (for example, a p-value) was not performed for this endpoint.

End point values	STP/VPA + GWP42003-P			
Subject group type	Reporting group			
Number of subjects analysed	30 ^[33]			
Units: subjects	0			

Notes:

[33] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: OLE: Number of subjects with vital sign findings indicative of an adverse event

End point title	OLE: Number of subjects with vital sign findings indicative of an adverse event ^[34]
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End point description:

Subjects were assessed for adverse events relating to vital signs at every visit.

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Primary
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End point timeframe:

Day 40 to Day 372

Notes:

[34] - 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 analysis (for example, a p-value) was not performed for this endpoint.

End point values	STP/VPA + GWP42003-P			
Subject group type	Reporting group			
Number of subjects analysed	30 ^[35]			
Units: subjects	0			

Notes:

[35] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: OLE: Number of subjects with 12-electrocardiogram (ECG) findings indicative of an adverse event

End point title	OLE: Number of subjects with 12-electrocardiogram (ECG) findings indicative of an adverse event ^[36]
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End point description:

After 5 minutes in a supine position, subjects were assessed for adverse events related to their 12-ECG results.

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Primary
End point timeframe:	
Day 40 to Day 372	

Notes:

[36] - 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 analysis (for example, a p-value) was not performed for this endpoint.

End point values	STP/VPA + GWP42003-P			
Subject group type	Reporting group			
Number of subjects analysed	30 ^[37]			
Units: subjects	1			

Notes:

[37] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: OLE: Number of subjects with a positive response to questions regarding suicidal behavior using the Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	OLE: Number of subjects with a positive response to questions regarding suicidal behavior using the Columbia-Suicide Severity Rating Scale (C-SSRS) ^[38]
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End point description:

The C-SSRS questionnaire is a brief, standardized measure that uniquely assesses the essential information (behavior, ideation, lethality, and severity) and distinguishes between suicidal occurrences and non-suicidal self-injury.

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Primary
End point timeframe:	
Day 40 to Day 372	

Notes:

[38] - 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 analysis (for example, a p-value) was not performed for this endpoint.

End point values	STP/VPA + GWP42003-P			
Subject group type	Reporting group			
Number of subjects analysed	30 ^[39]			
Units: subjects	0			

Notes:

[39] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: OLE: Change from Baseline in seizure frequency

End point title	OLE: Change from Baseline in seizure frequency ^[40]
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End point description:

Subjects recorded seizures in a diary throughout the trial. Seizure frequency was defined as the total number of seizures divided by the total number of reported days in the subject's diary. Any intermittent missing data for the number of seizures arising from unreported days in the diary were not imputed. Negative changes represent a decrease in frequency. Positive changes represent an increase in frequency.

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Primary
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End point timeframe:

Day 40 to Day 372

Notes:

[40] - 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 analysis (for example, a p-value) was not performed for this endpoint.

End point values	STP/VPA + GWP42003-P			
Subject group type	Reporting group			
Number of subjects analysed	22 ^[41]			
Units: subjects				
Change from Baseline, >25% increase	8			
Change from Baseline, -25% to 25% (no change)	4			
Change from Baseline, 25% to 50% decrease	6			
Change from Baseline, 50% to 75% decrease	3			
Change from Baseline, >75% decrease	1			

Notes:

[41] - Safety Analysis Set. Only participants with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: OLE: Number of subjects abusing IMP

End point title	OLE: Number of subjects abusing IMP ^[42]
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End point description:

Two types of events triggered the discussion of abuse potential with subjects - triggering AEs of special interest and/or drug accountability inconsistencies. A questionnaire was provided based on the triggering event and each case was reviewed by the Abuse Adjudication Committee.

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Primary
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End point timeframe:

Day 40 to Day 372

Notes:

[42] - 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 analysis (for example, a p-value) was not performed for this endpoint.

End point values	STP/VPA + GWP42003-P			
Subject group type	Reporting group			
Number of subjects analysed	30 ^[43]			
Units: subjects	0			

Notes:

[43] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: DN Cmax of 4-ene-VPA, CLB, N-CLB, LEV and TPM

End point title	Double Blind: DN Cmax of 4-ene-VPA, CLB, N-CLB, LEV and TPM
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End point description:

Cmax is the maximum measured plasma concentration. Blood samples were collected for PK analysis predose, 15 and 30 minutes, then 1, 1.5, 2, 4, 6, and 12 hours postdose.

998=a geometric coefficient of variation cannot be calculated for a single participant.

999=No analysis was conducted for this treatment arm at this time point. A subject may not have taken all anti-epileptic drugs.

n=number of subjects with evaluable data.

The PK analysis set includes all subjects enrolled in the trial who received at least 1 dose of GWP42003-P or placebo and who provided some on-treatment data.

End point type	Secondary
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End point timeframe:

Day 1 and Day 26

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[44]	2 ^[45]	12 ^[46]	3 ^[47]
Units: ng/mL/mg				
geometric mean (geometric coefficient of variation)				
4-ene-VPA Day 1 n=3,0,12,3	0.144 (± 27.0)	999 (± 999)	0.253 (± 102.7)	0.226 (± 39.0)
4-ene-VPA Day 26 n=2,0,10,3	0.129 (± 36.4)	999 (± 999)	0.182 (± 89.5)	0.19 (± 45.0)
CLB Day 1 n=4,0,3,0	61.5 (± 33.3)	999 (± 999)	25.9 (± 53.5)	999 (± 999)
CLB Day 26 n=3,0,3,0	73.4 (± 42.6)	999 (± 999)	28.2 (± 44.3)	999 (± 999)
N-CLB Day 1 n=4,0,3,0	508 (± 66.1)	999 (± 999)	71.6 (± 76.4)	999 (± 999)
N-CLB Day 26 n=3,0,3,0	790 (± 36.7)	999 (± 999)	292 (± 57.0)	999 (± 999)
LEV Day 1 n=0,1,0,0	999 (± 999)	31.6 (± 998)	999 (± 999)	999 (± 999)
LEV Day 26 n=0,1,0,0	999 (± 999)	38.9 (± 998)	999 (± 999)	999 (± 999)
TPM Day 1 n=2,0,1,0	65.1 (± 34.0)	999 (± 999)	87.7 (± 998)	999 (± 999)
TPM Day 26 n=2,0,1,0	60.7 (± 35.2)	999 (± 999)	738 (± 998)	999 (± 999)

Notes:

[44] - PK Analysis Set

[45] - PK Analysis Set

[46] - PK Analysis Set

[47] - PK Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: tmax of 4-ene-VPA, CLB, N-CLB, LEV and TPM

End point title	Double Blind: tmax of 4-ene-VPA, CLB, N-CLB, LEV and TPM
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End point description:

tmax is the time to the maximum measured plasma concentration. Blood samples were collected for PK analysis predose, 15 and 30 minutes, then 1, 1.5, 2, 4, 6, and 12 hours postdose.

998=a geometric coefficient of variation cannot be calculated for a single participant.

999=No analysis was conducted for this treatment arm at this time point. A subject may not have taken all anti-epileptic drugs.

n=number of subjects with evaluable data.

The PK analysis set includes all subjects enrolled in the trial who received at least 1 dose of GWP42003-P or placebo and who provided some on-treatment data.

End point type	Secondary
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End point timeframe:

Day 1 and Day 26

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[48]	2 ^[49]	12 ^[50]	3 ^[51]
Units: hours				
median (full range (min-max))				
4-ene-VPA Day 1 n=3,0,12,3	0.50 (0.25 to 4.03)	999 (999 to 999)	6.00 (0.25 to 12.48)	5.92 (4.00 to 6.00)
4-ene-VPA Day 26 n=2,0,10,3	3.67 (1.50 to 5.83)	999 (999 to 999)	1.73 (0.00 to 11.50)	3.85 (0.00 to 6.00)
CLB Day 1 n=4,0,3,0	5.06 (1.52 to 11.02)	999 (999 to 999)	2.33 (1.00 to 4.00)	999 (999 to 999)
CLB Day 26 n=3,0,3,0	6.03 (2.07 to 10.97)	999 (999 to 999)	1.00 (0.92 to 4.00)	999 (999 to 999)
N-CLB Day 1 n=4,0,3,0	5.03 (0.00 to 6.08)	999 (999 to 999)	1.50 (0.00 to 4.00)	999 (999 to 999)
N-CLB Day 26 n=3,0,3,0	2.00 (0.53 to 10.90)	999 (999 to 999)	4.00 (0.00 to 6.00)	999 (999 to 999)
LEV Day 1 n=0,1,0,0	999 (999 to 999)	1.00 (1.00 to 1.00)	999 (999 to 999)	999 (999 to 999)
LEV Day 26 n=0,1,0,0	999 (999 to 999)	1.00 (1.00 to 1.00)	999 (999 to 999)	999 (999 to 999)
TPM Day 1 n=2,0,1,0	3.04 (2.08 to 4.00)	999 (999 to 999)	1.50 (1.50 to 1.50)	999 (999 to 999)
TPM Day 26 n=2,0,0,0	2.03 (2.00 to 2.07)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)

Notes:

[48] - Safety Analysis Set

[49] - Safety Analysis Set

[50] - Safety Analysis Set

[51] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: DN AUCtau of 4-ene-VPA, CLB, N-CLB, LEV and TPM

End point title	Double Blind: DN AUCtau of 4-ene-VPA, CLB, N-CLB, LEV and TPM
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End point description:

AUCtau is the area under the concentration-time curve over the dosing interval. Blood samples were collected for PK analysis predose, 15 and 30 minutes, then 1, 1.5, 2, 4, 6, and 12 hours postdose.

999=No analysis was conducted for this treatment arm at this time point.

n=number of subjects with evaluable data.

The PK analysis set includes all subjects enrolled in the trial who received at least 1 dose of GWP42003-P or placebo and who provided some on-treatment data.

End point type	Secondary
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End point timeframe:

Day 1 and Day 26

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[52]	2 ^[53]	12 ^[54]	3 ^[55]
Units: ngxh/mL/mg				
geometric mean (geometric coefficient of variation)				
4-ene-VPA Day 1 n=3,0,12,3	1.34 (± 21.0)	999 (± 999)	2.54 (± 104.8)	2.35 (± 42.3)
4-ene-VPA Day 26 n=2,0,10,3	1.23 (± 40.4)	999 (± 999)	1.7 (± 103.3)	1.86 (± 42.2)
CLB Day 1 n=4,0,3,0	567 (± 38.1)	999 (± 999)	219 (± 61.3)	999 (± 999)
CLB Day 26 n=3,0,3,0	692 (± 42.4)	999 (± 999)	277 (± 47.7)	999 (± 999)
N-CLB Day 1 n=4,0,3,0	5100 (± 63.5)	999 (± 999)	744 (± 65.0)	999 (± 999)
N-CLB Day 26 n=3,0,3,0	7710 (± 35.5)	999 (± 999)	3200 (± 49.9)	999 (± 999)
LEV Day 1 n=0,1,0,0	999 (± 999)	222 (± 999)	999 (± 999)	999 (± 999)
LEV Day 26 n=0,0,0,0	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)
TPM Day 1 n=2,0,1,0	658 (± 29.9)	999 (± 999)	738 (± 999)	999 (± 999)
TPM Day 26 n=2,0,0,0	597 (± 27.6)	999 (± 999)	999 (± 999)	999 (± 999)

Notes:

[52] - PK Analysis Set

[53] - PK Analysis Set

[54] - PK Analysis Set

[55] - PK Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Number of subjects with Cytochrome P450 (CYP450) isoforms

End point title	Double Blind: Number of subjects with Cytochrome P450 (CYP450) isoforms ^[56]
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End point description:

Genetic testing was only conducted if specific consent was obtained from the patient or their legal representative. There was a separate ICF for this testing. Genetic testing was conducted to look at sequencing CYP450 isoforms, with particular focus on CYP2C19 and CYP3A4, involved in the metabolism of AEDs and CBD.

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Secondary
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End point timeframe:

Day 1

Notes:

[56] - 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 analysis (for example, a p-value) was not performed for this endpoint.

End point values	STP + GWP42003-P	VPA + GWP42003-P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12 ^[57]	16 ^[58]		
Units: subjects				
CYP3A4, Poor Metabolizer	0	0		
CYP3A4, Intermediate Metabolizer	1	0		
CYP3A4, Extensive Metabolizer	13	16		
CYP3A4, Ultrarapid Metabolizer	0	0		
CYP3A4, Undetermined	0	0		
CYP3A4, Missing	0	3		
CYP2C19, Poor Metabolizer	0	2		
CYP2C19, Intermediate Metabolizer	4	4		
CYP2C19, Extensive Metabolizer	6	5		
CYP2C19, Ultrarapid Metabolizer	4	4		
CYP2C19, Undetermined	0	1		
CYP2C19, Missing	0	3		

Notes:

[57] - Safety Analysis Set

[58] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Number of subjects with adverse events

End point title	Double Blind: Number of subjects with adverse events
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End point description:

An AE is 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 screening (Visit 1) and at any point up to the post treatment, safety follow-up visit (Visit 6 if patients did not enter the OLE or Visit 13 if they completed the OLE or 28 [\pm 3] days following the last dose of IMP), which may or may not have been considered to be related to the IMP. Results are categorized by system organ class and then by all-causality (any and all AEs, regardless of relation to IMP [investigational medicinal product]) and treatment-related (an AE marked as possibly attributed to IMP).

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Secondary
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End point timeframe:

Day 1 to Day 26

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[59]	2 ^[60]	16 ^[61]	4 ^[62]
Units: subjects				
Gastrointestinal Disorders, All-causality	6	0	11	0
Gastrointestinal Disorders, Treatment-related	6	0	11	0
General Disorders, All-causality	3	0	1	0
General Disorders, Treatment-related	3	0	0	0
Investigations, All-causality	2	0	2	0
Investigations, Treatment-related	2	0	2	0
Metabolic Disorders, All-causality	2	0	1	0
Metabolic Disorders, Treatment-related	2	0	1	0
Psychiatric Disorders, All-causality	2	0	1	0
Psychiatric, Treatment-related	2	0	1	0
Infections, All-causality	1	0	3	1
Infections, Treatment-related	0	0	0	0
Injury/Procedural Complications, All-causality	1	0	1	0
Injury/Procedural Complications, Treatment-related	0	0	0	0
Skin Disorders, All-causality	1	0	1	0
Skin Disorders, Treatment-related	1	0	0	0
Nervous System Disorders, All-causality	0	0	2	0
Nervous System Disorders, Treatment-related	0	0	2	0
Hepatobiliary Disorders, All-causality	0	0	1	0
Hepatobiliary Disorders, Treatment-related	0	0	1	0
Vascular Disorders, All-causality	0	0	1	0
Vascular Disorders, Treatment-related	0	0	1	0

Notes:

[59] - Safety Analysis Set

[60] - Safety Analysis Set

[61] - Safety Analysis Set

[62] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Number of subjects with shifts from normal in hematology laboratory values

End point title	Double Blind: Number of subjects with shifts from normal in hematology laboratory values
-----------------	--

End point description:

Results are categorized by the number of subjects with a shift from normal to low (N2L) or normal to high (N2H) at Visit 5 (V5, Day 40), Visit 6 (V6, Day 54), Visit 7 (V7, Day 82), Visit 8 (V8, Day 110), Visit 9 (V9, Day 194), Visit 10 (V10, Day 278), Visit 11 (V11, Day 362) and Visit 12 (V12, Day 372).

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Secondary
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End point timeframe:

Day 1 to Day 26

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[63]	2 ^[64]	16 ^[65]	4 ^[66]
Units: subjects				
V3, N2L, Neutrophils (%)	0	0	1	0
V3, N2L, Red Blood Cell Count	2	0	0	1
V3, N2L, Hematocrit	2	1	0	0
V3, N2L, Lymphocytes (%)	2	0	0	0
V3, N2H, Absolute Monocyte Count	1	0	1	2
V3, N2H, Lymphocytes (%)	0	0	2	0
V3, N2H, Absolute Neutrophil Count	1	0	0	0
V3, N2H, Eosinophils (%)	0	1	0	0
V3, N2H, Neutrophils (%)	2	0	0	0
V3, N2H, White Blood Cell Count with Differential	1	0	0	0
V4, N2L, Absolute Neutrophil Count	1	0	1	0
V4, N2L, Hematocrit	1	0	1	0
V4, N2L, Hemoglobin	1	0	0	0
V4, N2L, Lymphoblasts	1	0	1	0
V4, N2L, Lymphocytes (%)	3	0	0	0
V4, N2L, Neutrophils (%)	3	0	2	1
V4, N2L, Platelets	1	0	0	0
V4, N2L, Red Blood Cell Count	1	0	0	1
V4, N2L, White Blood Cell Count with Differential	1	0	0	0
V4, N2H, Absolute Eosinophil Count	1	0	1	0
V4, N2H, Absolute Monocyte Count	2	0	0	1
V4, N2H, Eosinophils (%)	3	0	2	0
V4, N2H, Lymphoblasts	1	0	0	0
V4, N2H, Lymphocytes (%)	2	0	3	0
V4, N2H, Neutrophils (%)	1	0	0	1
V4, N2H, Monocytes (%)	0	0	1	0
V5, N2H, Eosinophils (%)	1	0	0	0

Notes:

[63] - Safety Analysis Set

[64] - Safety Analysis Set

[65] - Safety Analysis Set

[66] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Number of subjects with shifts from normal in biochemistry laboratory values

End point title	Double Blind: Number of subjects with shifts from normal in biochemistry laboratory values
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End point description:

Results are categorized by the number of subjects with a shift from normal to low (N2L) or normal to

high (N2H) at Visit 5 (V5, Day 40), Visit 6 (V6, Day 54), Visit 7 (V7, Day 82), Visit 8 (V8, Day 110), Visit 9 (V9, Day 194), Visit 10 (V10, Day 278), Visit 11 (V11, Day 362) and Visit 12 (V12, Day 372).

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Secondary
End point timeframe:	
Day 1 to Day 26	

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[67]	2 ^[68]	16 ^[69]	4 ^[70]
Units: subjects				
V3, N2L, Total Bilirubin (blood)	2	1	1	1
V3, N2L, Total Protein (blood)	1	0	0	0
V3, N2L, Calcium	0	0	1	0
V3, N2L, Creatinine (Jaffe)	0	0	2	0
V3, N2L, HDL-Cholesterol	0	0	1	0
V3, N2L, Sodium	0	0	2	0
V3, N2H, ALT	1	0	1	0
V3, N2H, GGT	0	0	1	0
V3, N2H, Prolactin	0	0	0	1
V3, N2H, Total Bilirubin (blood)	0	0	1	0
V3, N2H, Triglycerides	0	0	1	0
V3, N2H, AST	1	0	0	0
V4, N2L, Alkaline Phosphatase	2	0	0	1
V4, N2L, Calcium	0	0	3	0
V4, N2L, Creatinine (Jaffe)	0	0	1	0
V4, N2L, Sodium	1	0	1	0
V4, N2L, Total Bilirubin (blood)	2	0	2	1
V4, N2L, Total Protein (blood)	0	0	1	0
V4, N2L, HDL-Cholesterol	1	0	0	0
V4, N2L, Urea Nitrogen	1	0	0	0
V4, N2H, ALT	2	0	5	0
V4, N2H, AST	2	0	3	1
V4, N2H, GGT	1	0	2	0
V4, N2H, HDL-Cholesterol	0	0	1	1
V4, N2H, Potassium	0	0	1	0
V4, N2H, Prolactin	1	0	0	1
V4, N2H, Sodium	0	0	0	1
V4, N2H, Total Bilirubin (blood)	0	0	1	0
V4, N2H, Alkaline Phosphatase	1	0	0	0
V4, N2H, Triglycerides	1	0	0	0
V5, N2H, ALT	1	0	0	0

Notes:

[67] - Safety Analysis Set

[68] - Safety Analysis Set

[69] - Safety Analysis Set

[70] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Number of subjects with shifts from normal in urinalysis laboratory values

End point title	Double Blind: Number of subjects with shifts from normal in urinalysis laboratory values
-----------------	--

End point description:

Results are categorized by the number of subjects with a shift from normal to low (N2L) or normal to high (N2H).

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Secondary
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End point timeframe:

Day 1 to Day 26

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[71]	2 ^[72]	16 ^[73]	4 ^[74]
Units: subjects				
N2L	0	0	0	0
N2H	0	0	0	0

Notes:

[71] - Safety Analysis Set

[72] - Safety Analysis Set

[73] - Safety Analysis Set

[74] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Number of subjects with physical examination findings indicative of an adverse event

End point title	Double Blind: Number of subjects with physical examination findings indicative of an adverse event
-----------------	--

End point description:

Subjects were assessed for adverse events during physical examinations at every visit.

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Secondary
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End point timeframe:

Day 1 to Day 26

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[75]	2 ^[76]	16 ^[77]	4 ^[78]
Units: subjects	0	0	0	0

Notes:

[75] - Safety Analysis Set

[76] - Safety Analysis Set

[77] - Safety Analysis Set

[78] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Number of subjects with vital sign findings indicative of an adverse event

End point title	Double Blind: Number of subjects with vital sign findings indicative of an adverse event
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End point description:

Subjects were assessed for adverse events relating to vital signs at every visit.

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Secondary
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End point timeframe:

Day 1 to Day 26

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[79]	2 ^[80]	16 ^[81]	4 ^[82]
Units: subjects	0	0	0	0

Notes:

[79] - Safety Analysis Set

[80] - Safety Analysis Set

[81] - Safety Analysis Set

[82] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Number of subjects with 12-ECG findings indicative of an adverse event

End point title	Double Blind: Number of subjects with 12-ECG findings indicative of an adverse event
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End point description:

After 5 minutes in a supine position, subjects were assessed for adverse events related to their 12-ECG results.

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Secondary
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End point timeframe:

Day 1 to Day 26

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[83]	2 ^[84]	16 ^[85]	4 ^[86]
Units: subjects	0	0	0	0

Notes:

[83] - Safety Analysis Set

[84] - Safety Analysis Set

[85] - Safety Analysis Set

[86] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Number of subjects with a positive response to questions regarding suicidal behavior using the Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Double Blind: Number of subjects with a positive response to questions regarding suicidal behavior using the Columbia-Suicide Severity Rating Scale (C-SSRS)
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End point description:

The C-SSRS questionnaire is a brief, standardized measure that uniquely assesses the essential information (behavior, ideation, lethality, and severity) and distinguishes between suicidal occurrences and non-suicidal self-injury.

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Secondary
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End point timeframe:

Day 1 to Day 26

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[87]	2 ^[88]	16 ^[89]	4 ^[90]
Units: subjects	0	0	0	0

Notes:

[87] - Safety Analysis Set

[88] - Safety Analysis Set

[89] - Safety Analysis Set

[90] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Change from Baseline in seizure frequency

End point title	Double Blind: Change from Baseline in seizure frequency
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End point description:

Subjects recorded seizures in a diary throughout the trial. Seizure frequency was defined as the total number of seizures divided by the total number of reported days in the subject's diary. Any intermittent missing data for the number of seizures arising from unreported days in the diary were not imputed. Negative changes represent a decrease in frequency. Positive changes represent an increase in frequency.

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Secondary
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End point timeframe:

Day 1 to Day 26

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[91]	2 ^[92]	16 ^[93]	4 ^[94]
Units: subjects				
Change from Baseline, >25% increase	2	0	4	1
Change from Baseline, -25% to 25% (no change)	3	0	3	1
Change from Baseline, 25% to 50% decrease	3	0	0	1
Change from Baseline, 50% to 75% decrease	2	0	3	0
Change from Baseline, >75% decrease	0	0	2	1

Notes:

[91] - Safety Analysis Set

[92] - Safety Analysis Set

[93] - Safety Analysis Set

[94] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Number of subjects abusing IMP

End point title	Double Blind: Number of subjects abusing IMP
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End point description:

Two types of events triggered the discussion of abuse potential with subjects - triggering AEs of special interest and/or drug accountability inconsistencies. A questionnaire was provided based on the triggering event and each case was reviewed by the Abuse Adjudication Committee.

The safety analysis set includes all subjects who received at least 1 dose of GWP42003-P or placebo.

End point type	Secondary
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End point timeframe:

Day 1 to Day 26

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[95]	2 ^[96]	16 ^[97]	4 ^[98]
Units: subjects	0	0	0	0

Notes:

[95] - Safety Analysis Set

[96] - Safety Analysis Set

[97] - Safety Analysis Set

[98] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: AUC(0-t) of 4-ene-VPA, CLB, N-CLB, LEV and TPM

End point title	Double Blind: AUC(0-t) of 4-ene-VPA, CLB, N-CLB, LEV and TPM
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End point description:

All the calculations were to be based on the first dosing period (tau); thus, analysis of AUC(0-t) was no longer planned.

End point type	Secondary
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End point timeframe:

Day 1 and Day 26

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[99]	0 ^[100]	0 ^[101]	0 ^[102]
Units: ngxh/mL/mg				
geometric mean (geometric coefficient of variation)	()	()	()	()

Notes:

[99] - Analysis of this endpoint was not conducted.

[100] - Analysis of this endpoint was not conducted.

[101] - Analysis of this endpoint was not conducted.

[102] - Analysis of this endpoint was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: AUC(0-t) for STP, VPA and CBD

End point title	Double Blind: AUC(0-t) for STP, VPA and CBD
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End point description:

All the calculations were to be based on the first dosing period (tau); thus, analysis of AUC(0-t) was no longer planned.

End point type	Secondary
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End point timeframe:

Day 1 and Day 26

End point values	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P	VPA + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[103]	0 ^[104]	0 ^[105]	0 ^[106]
Units: ngxh/mL/mg				
geometric mean (geometric coefficient of variation)	()	()	()	()

Notes:

[103] - Analysis of this endpoint was not conducted.

[104] - Analysis of this endpoint was not conducted.

[105] - Analysis of this endpoint was not conducted.

[106] - Analysis of this endpoint was not conducted.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to Day 418

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	STP + GWP42003-P
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Reporting group description:

On Day 2, subjects received an oral administration of GWP42003-P twice daily (morning and evening; immediately after the subject's stiripentol [STP] dose), commencing with up-titration of 100 milligrams per milliliter (mg/mL) GWP42003-P to a maintenance dose of 20 milligrams per kilogram per day (mg/kg/day) over 10 days (Days 2 to 11). After titration with GWP42003-P, subjects continued to take the maintenance dose of GWP42003-P for 14 days (Days 12 to 25). On Day 27, subjects either entered a tapering period (10% per day over 10 days) or, if the subject elected to participate in the open-label extension study, they entered a 10-day period of simultaneous tapering (of GWP42003-P) and titration (of GWP42003-P) in order to maintain blinding.

Reporting group title	STP + Placebo
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Reporting group description:

On Day 2, subjects received an oral administration of matching placebo twice daily (morning and evening; immediately after the subject's STP dose), commencing with up-titration of 100 mg/mL placebo to a maintenance dose of 20 mg/kg/day over 10 days (Days 2 to 11). After titration with placebo, subjects continued to take the maintenance dose of placebo for 14 days (Days 12 to 25). On Day 27, subjects either entered a tapering period (10% per day over 10 days) or, if the subject elected to participate in the open-label extension study, they entered a 10-day period of simultaneous tapering (of placebo) and titration (of placebo) in order to maintain blinding.

Reporting group title	VPA + GWP42003-P
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Reporting group description:

On Day 2, subjects received an oral administration of GWP42003-P twice daily (morning and evening; immediately after the subject's Valproate [VPA] dose), commencing with up-titration of 100 mg/mL GWP42003-P to a maintenance dose of 20 mg/kg/day over 10 days (Days 2 to 11). After titration with GWP42003-P, subjects continued to take the maintenance dose of GWP42003-P for 14 days (Days 12 to 25). On Day 27, subjects either entered a tapering period (10% per day over 10 days) or, if the subject elected to participate in the open-label extension study, they entered a 10-day period of simultaneous tapering (of GWP42003-P) and titration (of GWP42003-P) in order to maintain blinding.

Reporting group title	VPA + Placebo
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Reporting group description:

On Day 2, subjects received an oral administration of matching placebo twice daily (morning and evening; immediately after the subject's VPA dose), commencing with up-titration of 100 mg/mL placebo to a maintenance dose of 20 mg/kg/day over 10 days (Days 2 to 11). After titration with placebo, subjects continued to take the maintenance dose of placebo for 14 days (Days 12 to 25). On Day 27, subjects either entered a tapering period (10% per day over 10 days) or, if the subject elected to participate in the open-label extension study, they entered a 10-day period of simultaneous tapering (of placebo) and titration (of placebo) in order to maintain blinding.

Reporting group title	STP/VPA + GWP42003-P
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Reporting group description:

Subjects completing the DB period were invited to participate in the OLE period. Subjects taking GWP42003-P during the DB period maintained their dose throughout the transition from the DB period into the OLE period. Subjects who received placebo during the DB period titrated 10% over 10 days to reach their maximum tolerable dose not to exceed 20 mg/kg/day in the OLE period. All subjects continued their STP or VPA as per physician's orders.

Serious adverse events	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	0 / 2 (0.00%)	1 / 16 (6.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (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
Eosinophil count increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (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			
Status epilepticus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (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			
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (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
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed	1 / 12 (8.33%)	0 / 2 (0.00%)	0 / 16 (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
Metabolism and nutrition disorders			
Hypophagia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (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	VPA + Placebo	STP/VPA + GWP42003-P	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	5 / 30 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	3 / 30 (10.00%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	3 / 30 (10.00%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophil count increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Status epilepticus			
subjects affected / exposed	0 / 4 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	0 / 4 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypophagia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	STP + GWP42003-P	STP + Placebo	VPA + GWP42003-P
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 12 (66.67%)	0 / 2 (0.00%)	14 / 16 (87.50%)
Vascular disorders			
Peripheral coldness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Gynaecomastia			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	0 / 16 (0.00%) 0
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Apathy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Binge eating			
subjects affected / exposed	1 / 12 (8.33%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Bradyphrenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Irritability			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Listless			
subjects affected / exposed	1 / 12 (8.33%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Personality disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Stubbornness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 12 (16.67%)	0 / 2 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Ammonia increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			

subjects affected / exposed	2 / 12 (16.67%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Bacterial test positive			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Eyelid contusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Face injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Stoma site reaction			
subjects affected / exposed	1 / 12 (8.33%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Dropoling			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Dysarthria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Head titubation			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	1 / 16 (6.25%) 1
Seizure subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	1 / 16 (6.25%) 1
Somnolence subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	1 / 16 (6.25%) 1
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	0 / 16 (0.00%) 0
Eye disorders Eczema eyelids subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	0 / 16 (0.00%) 0
Eyelid haematoma subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	0 / 16 (0.00%) 0
Gastrointestinal disorders Abnormal faeces subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 2 (0.00%) 0	0 / 16 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	0 / 16 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	5 / 12 (41.67%) 6	0 / 2 (0.00%) 0	11 / 16 (68.75%) 22
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	0 / 16 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 3	0 / 2 (0.00%) 0	2 / 16 (12.50%) 2
Salivary hypersecretion			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	0 / 16 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 0	0 / 2 (0.00%) 0	1 / 16 (6.25%) 1
Fatigue subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 3	0 / 2 (0.00%) 0	0 / 16 (0.00%) 0
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	0 / 16 (0.00%) 0
Eczema subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	0 / 16 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	0 / 16 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	1 / 16 (6.25%) 1
Skin lesion subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	0 / 16 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	0 / 16 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 2 (0.00%) 0	0 / 16 (0.00%) 0
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 2 (0.00%) 0	2 / 16 (12.50%) 2
Pharyngitis			

subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 12 (16.67%)	0 / 2 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Fluid intake reduced			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Increased appetite			
subjects affected / exposed	0 / 12 (0.00%)	0 / 2 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	VPA + Placebo	STP/VPA + GWP42003-P	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	25 / 30 (83.33%)	
Vascular disorders			
Peripheral coldness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	

Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Apathy			
subjects affected / exposed	0 / 4 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Binge eating			
subjects affected / exposed	0 / 4 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Bradyphrenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Irritability			
subjects affected / exposed	0 / 4 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	6	
Listless			
subjects affected / exposed	0 / 4 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Personality disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Stubbornness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Ammonia increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Bacterial test positive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Eyelid contusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Face injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Stoma site reaction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Drooling			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Dysarthria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	3	

Head titubation subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 30 (0.00%) 0	
Seizure subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	5 / 30 (16.67%) 5	
Somnolence subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 30 (6.67%) 3	
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 30 (3.33%) 1	
Eye disorders Eczema eyelids subjects affected / exposed occurrences (all) Eyelid haematoma subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0	1 / 30 (3.33%) 1 1 / 30 (3.33%) 1	
Gastrointestinal disorders Abnormal faeces subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Salivary hypersecretion	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0	0 / 30 (0.00%) 0 1 / 30 (3.33%) 1 17 / 30 (56.67%) 60 1 / 30 (3.33%) 2 2 / 30 (6.67%) 2	

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 30 (3.33%) 1	
Vomiting subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 30 (0.00%) 0	
Fatigue subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	4 / 30 (13.33%) 4	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 30 (6.67%) 2	
Eczema subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 30 (3.33%) 1	
Erythema subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 30 (3.33%) 1	
Rash subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 30 (0.00%) 0	
Skin lesion subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 30 (3.33%) 1	
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 30 (3.33%) 1	
Pain in extremity subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 30 (6.67%) 2	
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 30 (6.67%) 4	
Pharyngitis			

subjects affected / exposed	1 / 4 (25.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Fluid intake reduced			
subjects affected / exposed	0 / 4 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Increased appetite			
subjects affected / exposed	0 / 4 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 July 2016	<ul style="list-style-type: none">• All subjects were required to remain in the clinic for at least 30 minutes following administration of GWP42003-P at Visit 2 (Day 2) and Visit 4 (Day 27) to monitor for any adverse reactions, as this may have been the first exposure to the trial drug;• PK analysis of plasma levels of 4-ene-VPA was carried out along with AED (antiepileptic drugs) tests. No further blood sampling would be required in order to perform this analysis;• Clarification on the order of PK samples with respect to dosing of AEDs or IMP;• Sites (or caregiver, where appropriate) were required to record the times at which patients were fed at Visit 2 (Day 2) and Visit 4 (Day 27) for PK purposes;• Visits were provided in weeks rather than months for clarity;• Addition of exclusion criterion: Patient has a prolonged QTcB (the QT interval corrected for heart rate with Bazett correction) (> 450 msec for males and > 470 msec for females) [if right bundle branch block is present, QTcB limit is > 480 msec]. Exclusion criterion was added as a safety precaution as a formal QTc (QT interval corrected for heart rate) trial had not yet been completed with GWP42003-P;• Addition of withdrawal criterion: Significant change from baseline 12-lead electrocardiogram (ECG) in QTcB (> 60 msec) or absolute QTcB of > 500 msec. If right bundle branch block is present, absolute QTcB is 520 msec. Withdrawal criterion was added as a safety precaution as a formal QTc trial has not yet been completed with GWP42003-P;• The clinical trial GWEP1332 Part A Data Safety Monitoring Committee recommended dose has been amended from 25 mg/kg to 20 mg/kg due to an error in the original protocol.
20 July 2016	<ul style="list-style-type: none">• The titration of dose increases above 20 mg/kg/day was changed. Dose increases were recommended to be done slowly, with maximum increments of 2.5 mg/kg every 5 to 7 days. The investigator could schedule additional clinic visits during the OLE period to facilitate dose adjustments. This change in requirement was added as a safety precaution;• A benefit/risk section was added to the protocol, as per regulatory guidelines, and additional references included as applicable;• The physical description of the IMP was updated to "clear, colorless to yellow".• Additional text was added to clarify the process for confirming laboratory results for potential cases of drug-induced liver injury;• Additional text was added to clarify that instructions regarding IMP home storage requirements and dosing instructions would be provided to patients or their caregivers;• List of abbreviations was updated to include all abbreviations in the protocol;• References were updated to reflect the latest safety information;• Typographical, formatting, and consistency issues errors amended where applicable.
26 July 2016	<ul style="list-style-type: none">• Due to an error in the previous protocol version, the exclusion and withdrawal criteria relating to prolonged QTcB (the QT interval corrected for heart rate with Bazett correction) and significant change from baseline 12-lead ECG in QTcB or absolute QTcB were updated for clarity.

11 May 2017	<ul style="list-style-type: none"> • The amount of Δ^9-tetrahydrocannabinol in the IMP was more accurately described in the latest investigator's brochure. It was previously stated to be 0.5%; however, in the oral solution, it is actually $\leq 0.15\%$; • Two pivotal phase 3 clinical trials had completed since the GWEP1447 protocol was written, so the rationale was updated to reflect this; • Protocol was updated with information from the latest Development Core Safety Information dated 17-FEB-17; • The blood sample for the 24-hour PK time point was removed as it does not provide any additional information that cannot be obtained from the 12-hour sample. Removing this PK sample eliminated the need for an overnight stay for the patients in the clinic or a return visit the next day. It also removed the additional blood draw burden on the patients and was anticipated to aid recruitment. This change affected various sections of the protocol, which were updated accordingly; • The 30-minute observation period after the first dose of GWP42003-P was removed. Based on experience from randomized clinical trials, there was no evidence for this requirement of additional monitoring of patients after the first dose of GWP42003-P; • The primary PK parameter $AUC_{0-\infty}$ was replaced with AUC_{tau}. This is because the dosing was twice daily, and therefore, only AUC_{tau} was required; no further information would be gained from the 24-hour time point; • As the 24-hour PK time point was removed, it would no longer be possible to accurately determine the $t_{1/2}$ of the drug, so the $t_{1/2}$ PK parameter was also removed; • Reference to CBD metabolites and THC and THC metabolites was removed as these have been fully characterized in other trials. CBD is the perpetrator drug in this trial, and therefore, only the parent drug needed to be reported and analyzed to check for compliance.
11 May 2017	<ul style="list-style-type: none"> • An update was added to allow database lock and analysis of either the VPA or STP arm first, if 1 arm completed recruitment before the other; • There were various sections throughout the GWEP1447 protocol and in the abbreviations that pertained only to clinical trials conducted in France. Since there was a France-specific protocol (GWEP1447 Version 5 28Jul16) for this trial, the text was removed; • The medical monitor that was listed had left GW, so the contact information for the new medical monitor was added. Also, to ensure that all relevant GW medical personnel were notified of any issues, the common medical monitor e-mail address was added.
04 June 2018	<ul style="list-style-type: none"> • The protocol provided for pregnancy testing at Visit 1 for females of childbearing potential. The amendment implemented additional monthly (4 weekly) pregnancy tests at clinic visits or at home throughout the blinded and open-label phases of the trial; • The sample size of the STP arm was reduced from 20 to 14 patients; • There was an error in the protocol because there was no objective linked to the secondary endpoint mentioned in the protocol. To correct this error, Section 1 (Protocol Synopsis) and Section 2.2 (Secondary Objectives) of the protocol were updated to include the following secondary objective: <ul style="list-style-type: none"> • To assess whether GWP42003-P affects the PK profile of 4-ene-VPA, CLB, N-CLB, LEV, TPM in patients also being treated with STP or VPA and other AEDs; • The classification of increased appetite was changed from "the most common adverse events ($> 10\%$ all-causality)" to "common (1-10%)."; • To accommodate the amended text, minor updates were made to the original text in other locations in the document to maintain internal consistency/style, and other typographical errors were amended where applicable.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported