Clinical trial results:
A double-blind, randomised, placebo-controlled, parallel group study of GWP42003 as adjunctive therapy in the first line treatment of schizophrenia or related psychotic disorder

Summary

EudraCT number	2013-000212-22
Trial protocol	GB PL RO
Global end of trial date	08 January 2015

Results information

Result version number	v1 (current)
This version publication date	09 February 2019
First version publication date	09 February 2019

Trial information

Trial identification

Sponsor protocol code	GWAP1241

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02006628
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	Alternate contact: medinfo@greenwichbiosciences.com, GW Research Ltd, +44 1223 238170, medinfo@gwpharm.com
Scientific contact	Alternate contact: medinfo@greenwichbiosciences.com, GW Research Ltd, +44 1223 238170, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 January 2015
Global end of trial reached?	Yes
Global end of trial date	08 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of GWP42003 as an adjunctive therapy to first line treatment in alleviating symptoms of schizophrenia or related psychotic disorder compared with placebo on the following non-comprehensive list of assessments:
- Positive and Negative Syndrome Scale (PANSS) total score
- PANSS P, N, & G scores
- Scale for the Assessment of Negative Symptoms (SANS) score
- Clinical assessment of (change in) mental state (CGI-S & CGI-I, respectively)
- Brief Assessment of Cognition in Schizophrenia (BACS)
- Assess safety & tolerability of GWP42003 as adjunctive therapy

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted. No study procedures were performed on study candidates until written consent had been obtained from the participant. The informed consent form, protocol, and amendments for this study were submitted to and approved by the institutional review board or independent ethics committee at each participating study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 February 2014
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	Poland: 37
Country: Number of subjects enrolled	Romania: 40
Country: Number of subjects enrolled	United Kingdom: 11
Worldwide total number of subjects	88
EEA total number of subjects	88

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)	0
Adults (18-64 years)	88
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This was a multi-center, double-blind, randomised, placebo-controlled, parallel group study of GWP42003 1000 milligrams (mg)/day compared to placebo; 6-week treatment study period followed by a 2-week follow-up period. Eligible participants entered the study at a Screening and Randomisation Visit (Day 1), where eligibility was established.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	GWP42003 1000 mg/day

Arm description:

Participants received GWP42003 (100 mg/mL), 5 mL twice daily (BID) administered orally, 5 mL in the morning and 5 mL in the evening for 6 weeks.

Arm type	Experimental
Investigational medicinal product name	GWP42003
Investigational medicinal product code	
Other name	Cannabidiol
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

GWP42003 was presented as an oral solution containing 100 mg/mL cannabidiol (CBD) dissolved in the excipients sesame oil and anhydrous ethanol with added sweetener and strawberry flavoring.

Arm title	Placebo

Arm description:

Participants received placebo (0 mL cannabidiol [CBD]), volume matched to the 5 mL BID dose level, administered orally, 5 mL in the morning and 5 mL in the evening for 6 weeks.

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

Dosage and administration details:

Participants received placebo (0 mg/mL CBD) dissolved in the excipients sesame oil and anhydrous ethanol with added sweetener and strawberry flavoring.

Number of subjects in period 1	GWP42003 1000 mg/day	Placebo
Started	43	45
Received at Least 1 Dose of Study Drug	43	45
Completed	40	43
Not completed	3	2
Consent withdrawn by subject	2	1
Adverse event, non-fatal	1	1

Baseline characteristics

Reporting groups	
Reporting group title	GWP42003 1000 mg/day
Reporting group description:	
Participants received GWP42003 (100 mg/mL), 5 mL twice daily (BID) administered orally, 5 mL in the morning and 5 mL in the evening for 6 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo (0 mL cannabidiol [CBD]), volume matched to the 5 mL BID dose level, administered orally, 5 mL in the morning and 5 mL in the evening for 6 weeks.	

Reporting group values	GWP42003 1000 mg/day	Placebo	Total
Number of subjects	43	45	88
Age categorical Units: Subjects			
Adults (18-64 years)	43	45	88
Age continuous Units: years			
arithmetic mean	40.9	40.8	
standard deviation	± 12.49	± 11.00	-
Gender categorical Units: Subjects			
Female	15	22	37
Male	28	23	51

End points

End points reporting groups

Reporting group title	GWP42003 1000 mg/day
Reporting group description:	
Participants received GWP42003 (100 mg/mL), 5 mL twice daily (BID) administered orally, 5 mL in the morning and 5 mL in the evening for 6 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo (0 mL cannabidiol [CBD]), volume matched to the 5 mL BID dose level, administered orally, 5 mL in the morning and 5 mL in the evening for 6 weeks.	

Primary: Change From Baseline To End Of Treatment (Day 43) In Positive And Negative Syndrome Scale (PANSS) Total Score

End point title	Change From Baseline To End Of Treatment (Day 43) In Positive And Negative Syndrome Scale (PANSS) Total Score
End point description:	
The PANSS was a 30-item medical scale completed by a trained rater that assessed the positive and negative symptoms of schizophrenia as well as symptoms of general psychopathology. The PANSS Total score was derived from the sum of the 30 items, which were rated on a 7-point scale, where 1 = absent and 7 = extreme. The total score is the summed total for each of the PANSS positive symptom ('P'), negative symptom ('N'), general psychopathology symptom ('G') scores and could range from 30 to 210 points, with lower scores equating to milder severity of symptoms, that is, closer to psychologically normal.	
End point type	Primary
End point timeframe:	
Day 1 through Day 43	

End point values	GWP42003 1000 mg/day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	44		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline Score	79.3 (± 12.45)	80.6 (± 14.90)		
End of Treatment score	68.1 (± 14.79)	71.9 (± 15.49)		
Change from baseline	-11.2 (± 7.87)	-8.8 (± 8.87)		

Statistical analyses

Statistical analysis title	GWP42003 1000 mg/day, Placebo
Comparison groups	Placebo v GWP42003 1000 mg/day

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1332
Method	ANCOVA
Parameter estimate	Treatment difference (GWP42003-placebo)
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	0.9

Primary: Change From Baseline To The End Of Treatment (Day 43) In PANSS 'P' Score

End point title	Change From Baseline To The End Of Treatment (Day 43) In PANSS 'P' Score

End point description:

The PANSS 'P' scale measured the severity of positive symptoms, including delusions, conceptual disorganisation, hallucinations, hyperactivity, grandiosity, suspiciousness/persecution, and hostility. Individual items were rated on a 7-point scale, where 1 = absent and 7 = extreme. The total 'P' score could range from 7 to 49 points, with lower scores equating to milder severity of symptoms, that is, closer to psychologically normal.

End point type	Primary

End point timeframe:

Day 1 through Day 43

End point values	GWP42003 1000 mg/day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	44		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline score	18.0 (± 3.89)	17.5 (± 3.29)		
End of Treatment score	14.8 (± 4.01)	15.7 (± 3.73)		
Change from Baseline	-3.2 (± 2.60)	-1.7 (± 2.76)		

Statistical analyses

Statistical analysis title	GWP42003 1000 mg/day, Placebo
Comparison groups	Placebo v GWP42003 1000 mg/day

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0188
Method	ANCOVA
Parameter estimate	Treatment difference (GWP42003-placebo)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	-0.2

Primary: Change From Baseline To The End Of Treatment (Day 43) In PANSS 'N' Score

End point title	Change From Baseline To The End Of Treatment (Day 43) In PANSS 'N' Score

End point description:

The PANSS 'N' scale measured the severity of negative symptoms, including blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. Individual items were rated on a 7-point scale, where 1 = absent and 7 = extreme. The total 'N' score could range from 7 to 49 points, with lower scores equating to milder severity of symptoms, that is, closer to psychologically normal.

End point type	Primary

End point timeframe:

Day 1 through Day 43

End point values	GWP42003 1000 mg/day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	44		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline score	22.6 (± 5.04)	23.4 (± 5.11)		
End of Treatment score	19.9 (± 5.32)	20.5 (± 5.22)		
Change from Baseline	-2.7 (± 3.55)	-2.9 (± 3.06)		

Statistical analyses

Statistical analysis title	GWP42003 1000 mg/day, Placebo
Comparison groups	GWP42003 1000 mg/day v Placebo

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9647
Method	ANCOVA
Parameter estimate	Treatment difference (GWP42003-placebo)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	1.4

Primary: Change From Baseline To The End Of Treatment (Day 43) In PANSS 'G' Score

End point title	Change From Baseline To The End Of Treatment (Day 43) In PANSS 'G' Score

End point description:

The PANSS 'G' scale measured the severity of general psychopathology symptoms, including somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgement and insight, disturbance of violation, poor impulse control, preoccupation, and active social avoidance. Individual items were rated on a 7-point scale, where 1 = absent and 7 = extreme. The total 'G' score could range from 16 to 112 points, with lower scores equating to milder severity of symptoms, that is, closer to psychologically normal.

End point type	Primary

End point timeframe:

Day 1 through Day 43

End point values	GWP42003 1000 mg/day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	44		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline score	38.7 (± 6.71)	39.7 (± 8.95)		
End of Treatment score	33.4 (± 7.69)	35.6 (± 9.04)		
Change from Baseline	-5.3 (± 4.34)	-4.1 (± 4.78)		

Statistical analyses

Statistical analysis title	GWP42003 1000 mg/day, Placebo
Comparison groups	GWP42003 1000 mg/day v Placebo

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1963
Method	ANCOVA
Parameter estimate	Treatment difference (GWP42003-placebo)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	0.7

Primary: Change From Baseline To The End Of Treatment (Day 43) In The Scale For The Assessment Of Negative Symptoms (SANS)

End point title	Change From Baseline To The End Of Treatment (Day 43) In The Scale For The Assessment Of Negative Symptoms (SANS)

End point description:

The SANS assessed 5 symptom complexes to obtain clinical ratings of negative symptoms in participants with schizophrenia or related psychotic disorder. Symptom complexes were affective blunting, alogia (impoverished thinking), avolition/apathy, anhedonia/asociality, and disturbance of attention. Assessments were conducted on a 6-point scale (0 = not at all; 5 = severe). The total score could range from 0 to 125 points, with lower scores equating to milder severity of symptoms, that is, closer to psychologically normal.

End point type	Primary

End point timeframe:

Day 1 through Day 43

End point values	GWP42003 1000 mg/day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	44		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline score	52.8 (± 17.10)	55.3 (± 16.24)		
End of Treatment score	43.6 (± 16.54)	48.4 (± 15.75)		
Change from Baseline	-9.1 (± 13.09)	-6.3 (± 8.54)		

Statistical analyses

Statistical analysis title	GWP42003 1000 mg/day, Placebo
Comparison groups	GWP42003 1000 mg/day v Placebo

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1167
Method	ANCOVA
Parameter estimate	Treatment difference (GWP42003-placebo)
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.9
upper limit	0.9

Primary: Change From Baseline To The End Of Treatment (Day 43) In The Clinical Global Impression Severity Scale (CGI-S)

End point title	Change From Baseline To The End Of Treatment (Day 43) In The Clinical Global Impression Severity Scale (CGI-S)

End point description:

The CGI-S was a 7-point scale that required the clinician to rate the severity of a participant's illness at the time of assessment, relative to the clinician's past experience of participants who had the same diagnosis. Considering total clinical experience, participants were assessed on severity of mental illness at the time of rating on the following scale: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; or 7 = extremely ill. Lower scores equated to milder severity of symptoms, that is, closer to psychologically normal.

End point type	Primary

End point timeframe:

Day 1 through Day 43

End point values	GWP42003 1000 mg/day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	44		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline score	4.0 (± 0.70)	4.0 (± 0.65)		
End of Treatment score	3.5 (± 1.09)	3.8 (± 0.78)		
Change from Baseline	-0.5 (± 0.74)	-0.3 (± 0.49)		

Statistical analyses

Statistical analysis title	GWP42003 1000 mg/day, Placebo
Comparison groups	GWP42003 1000 mg/day v Placebo

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0443
Method	ANCOVA
Parameter estimate	Treatment difference (GWP42003-placebo)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0

Primary: Clinical Global Impression Improvement Scale (CGI-I) Values At Day 8 And End Of Treatment (Day 43)

End point title	Clinical Global Impression Improvement Scale (CGI-I) Values At Day 8 And End Of Treatment (Day 43)

End point description:

The CGI-I was a 7-point scale that required the clinician to assess how much a participant's illness had improved or worsened relative the first assessment at the beginning of the intervention. This was rated on the following scale: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; or 7 = very much worse. Lower scores equated to improvement of symptoms.

End point type	Primary

End point timeframe:

Day 8 through Day 43

End point values	GWP42003 1000 mg/day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	44		
Units: score on a scale				
arithmetic mean (standard deviation)				
Day 8 score	3.6 (± 0.50)	3.8 (± 0.56)		
End of Treatment score	2.9 (± 0.89)	3.4 (± 0.87)		

Statistical analyses

Statistical analysis title	GWP42003 1000 mg/day, Placebo
Comparison groups	GWP42003 1000 mg/day v Placebo

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0182
Method	ANCOVA
Parameter estimate	Treatment difference (GWP42003-placebo)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.1

Primary: Change From Baseline To The End Of Treatment (Day 43) In Brief Assessment Of Cognition In Schizophrenia (BACS) Score

End point title	Change From Baseline To The End Of Treatment (Day 43) In Brief Assessment Of Cognition In Schizophrenia (BACS) Score

End point description:

The BACS was an instrument used to assess the aspects of cognition found to be most impaired and most strongly correlated with outcome in participants with schizophrenia or related psychotic disorder. The BACS consisted of 6 domains: verbal memory (score range 0 to 75), working memory (score range 0 to 28), motor speed (score range 0 to 100), verbal fluency (score > 0), attention and speed of information processing (score range 0 to 110), and executive functions (score range 0 to 22). A score was obtained for each domain and a composite summary score was also calculated as the average of the scores from the 6 domains. An increase in score was indicative of an improvement in cognition.

End point type	Primary

End point timeframe:

Day 1 through Day 43

End point values	GWP42003 1000 mg/day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	44		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline score	32.21 (± 6.042)	32.91 (± 7.158)		
End of Treatment score	35.73 (± 6.981)	35.05 (± 7.310)		
Change from Baseline	3.48 (± 3.031)	2.14 (± 3.442)		

Statistical analyses

Statistical analysis title	GWP42003 1000 mg/day, Placebo
Comparison groups	GWP42003 1000 mg/day v Placebo

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0677
Method	ANCOVA
Parameter estimate	Treatment difference (GWP42003-placebo)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	2.72

Primary: Percentage Of PANSS Total Score Responders At End Of Treatment (Day 43)

End point title	Percentage Of PANSS Total Score Responders At End Of Treatment (Day 43)

End point description:

The percentage of PANSS treatment responders, defined as participants with ≥20% improvement in PANSS total score between baseline and End of Treatment (Day 43), is presented. The percentage of participants was calculated by dividing the number of participants with a ≥20% improvement in PANSS total score (yes) by the total number of participants.

End point type	Primary

End point timeframe:

Day 1 through Day 43

End point values	GWP42003 1000 mg/day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	44		
Units: participants				
Yes	12	6		
No	30	38		

Statistical analyses

Statistical analysis title	GWP42003 1000 mg/day, Placebo
Comparison groups	GWP42003 1000 mg/day v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0896 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	8

Notes:

[1] - Responder (yes/no) is the dependent variable with treatment included as a factor and age and baseline PANSS, G, and N scores included as covariates.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1 through Day 57	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	GWP42003 1000 mg/day
Reporting group description: Participants received GWP42003 (100 mg/mL), 5 mL BID administered orally, 5 mL in the morning and 5 mL in the evening for 6 weeks.	
Reporting group title	Placebo
Reporting group description: Participants received placebo (0 mL cannabidiol [CBD]), volume matched to the 5 mL BID dose level, administered orally, 5 mL in the morning and 5 mL in the evening for 6 weeks.	

Serious adverse events	GWP42003 1000 mg/day	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)	1 / 45 (2.22%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	GWP42003 1000 mg/day	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 43 (18.60%)	10 / 45 (22.22%)	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 43 (6.98%)	4 / 45 (8.89%)	
occurrences (all)	3	4	
Somnolence			

subjects affected / exposed	0 / 43 (0.00%)	3 / 45 (6.67%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 43 (9.30%)	2 / 45 (4.44%)	
occurrences (all)	4	2	
Nausea			
subjects affected / exposed	3 / 43 (6.98%)	0 / 45 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 43 (0.00%)	2 / 45 (4.44%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2014	The amendment to this study included updates to study objectives and endpoints to better reflect the exploratory nature of the Phase 2a study. Study objectives were combined rather than being separated into primary and secondary objectives. The study endpoints were then designated as "key" and "non-key" endpoints, based on their importance to the treatment of schizophrenia in this participant population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29241357