



## Clinical trial results:

### A Randomized, Double-Blind, Placebo-Controlled Trial to Investigate the Efficacy and Safety of Cannabidiol Oral Solution (GWP42003-P, CBD-OS) in Patients with Rett Syndrome.

#### Summary

EudraCT number	2018-003370-27
Trial protocol	GB IT
Global end of trial date	21 January 2021

#### Results information

Result version number	v1 (current)
This version publication date	05 August 2021
First version publication date	05 August 2021

#### Trial information

##### Trial identification

Sponsor protocol code	GWND18064
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03848832
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)	Yes
EMA paediatric investigation plan number(s)	EMA-001964-PIP02-19
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	21 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 January 2021
Global end of trial reached?	Yes
Global end of trial date	21 January 2021
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effect of GWP42003-P (Cannabidiol; CBD), compared with placebo, at the end of 24 weeks' treatment in reducing symptom severity in subjects with Rett syndrome using the Rett Syndrome Behaviour Questionnaire (RSBQ).

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 The International Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice (EMA/CHMP/ICH/135/1995) and the European Clinical Trial Directive 2001/20/EC. The ICH 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 British, Spanish and United States laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 July 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United States: 15
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	29
EEA total number of subjects	9

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)	18
Adolescents (12-17 years)	8
Adults (18-64 years)	3
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 41 subjects were screened for eligibility; 29 were randomized to the study treatments, and 12 were screen failures.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	5 mg/kg/day GWP42003-P

Arm description:

Subjects received 5 milligrams (mg)/kilogram (kg)/day GWP42003-P, administered as 100 mg/milliliter (mL) oral solution twice daily (BID).

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

Dosage and administration details:

GWP42003-P was administered orally in a fed state.

<b>Arm title</b>	15 mg/kg/day GWP42003-P
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Arm description:

Subjects received 15 mg/kg/day GWP42003-P, administered as 100 mg/mL oral solution BID.

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

Dosage and administration details:

GWP42003-P was administered orally in a fed state.

<b>Arm title</b>	Placebo
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Arm description:

Subjects received placebo oral solution matched to 5 or 15 mg/kg/day GWP42003-P, BID.

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

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**Dosage and administration details:**

The matching placebo oral solution was administered in a fed state.

<b>Number of subjects in period 1</b>	<b>5 mg/kg/day GWP42003-P</b>	<b>15 mg/kg/day GWP42003-P</b>	<b>Placebo</b>
Started	10	9	10
Completed	7	6	4
Not completed	3	3	6
Physician decision	2	1	3
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	1	-	-
Sponsor Decision - Covid-19 Precaution	-	-	1
Withdrawal Of Consent Due To Covid-19	-	-	1
Withdrawal (Covid-19)	-	2	-

## Baseline characteristics

### Reporting groups

Reporting group title	Period 1
Reporting group description: -	

Reporting group values	Period 1	Total	
Number of subjects	29	29	
Age categorical			
Units: subjects			
<=18 years	29	29	
Between 18 and 65 years	0	0	
>=65 years	0	0	
Age continuous			
Units: years			
arithmetic mean	9.7		
standard deviation	± 5.11	-	
Gender categorical			
Units: subjects			
Female	29	29	
Male	0	0	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	28	28	
More than one race	0	0	
Unknown or Not Reported	0	0	

### Subject analysis sets

Subject analysis set title	5 mg/kg/day GWP42003-P
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Analysis Set: All subjects who received at least 1 dose of investigational medicinal product in the trial were included and analyzed according to the treatment received. One subject who was assigned to the placebo group received GWP42003-P 5 mg/kg. For baseline analyses, this subject was assigned to the GWP42003-P 5 mg/kg group.

Subject analysis set title	15 mg/kg/day GWP42003-P
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Analysis Set: All subjects who received at least 1 dose of investigational medicinal product in the trial were included and analyzed according to the treatment received.

Subject analysis set title	Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Analysis Set: All subjects who received at least 1 dose of investigational medicinal product in the

trial were included and analyzed according to the treatment received. One subject who was assigned to the placebo group received GWP42003-P 5 mg/kg. For baseline analyses, this subject was assigned to the GWP42003-P 5 mg/kg group.

<b>Reporting group values</b>	<b>5 mg/kg/day GWP42003-P</b>	<b>15 mg/kg/day GWP42003-P</b>	<b>Placebo</b>
Number of subjects	11	9	9
Age categorical Units: subjects			
<=18 years	11	9	9
Between 18 and 65 years	0	0	0
>=65 years	0	0	0
Age continuous Units: years			
arithmetic mean	9.7	10.7	8.6
standard deviation	± 6.02	± 3.64	± 5.53
Gender categorical Units: subjects			
Female	11	9	9
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	10	9	9
More than one race	0	0	0
Unknown or Not Reported	0	0	0

## End points

### End points reporting groups

Reporting group title	5 mg/kg/day GWP42003-P
Reporting group description: Subjects received 5 milligrams (mg)/kilogram (kg)/day GWP42003-P, administered as 100 mg/milliliter (mL) oral solution twice daily (BID).	
Reporting group title	15 mg/kg/day GWP42003-P
Reporting group description: Subjects received 15 mg/kg/day GWP42003-P, administered as 100 mg/mL oral solution BID.	
Reporting group title	Placebo
Reporting group description: Subjects received placebo oral solution matched to 5 or 15 mg/kg/day GWP42003-P, BID.	
Subject analysis set title	5 mg/kg/day GWP42003-P
Subject analysis set type	Safety analysis
Subject analysis set description: Safety Analysis Set: All subjects who received at least 1 dose of investigational medicinal product in the trial were included and analyzed according to the treatment received. One subject who was assigned to the placebo group received GWP42003-P 5 mg/kg. For baseline analyses, this subject was assigned to the GWP42003-P 5 mg/kg group.	
Subject analysis set title	15 mg/kg/day GWP42003-P
Subject analysis set type	Safety analysis
Subject analysis set description: Safety Analysis Set: All subjects who received at least 1 dose of investigational medicinal product in the trial were included and analyzed according to the treatment received.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description: Safety Analysis Set: All subjects who received at least 1 dose of investigational medicinal product in the trial were included and analyzed according to the treatment received. One subject who was assigned to the placebo group received GWP42003-P 5 mg/kg. For baseline analyses, this subject was assigned to the GWP42003-P 5 mg/kg group.	

### Primary: Change from Baseline in the Mean Rett Syndrome Behaviour Questionnaire (RSBQ) Total Score at Week 24 for the 15 mg/kg/day GWP42003-P Dose Level Compared with Placebo

End point title	Change from Baseline in the Mean Rett Syndrome Behaviour Questionnaire (RSBQ) Total Score at Week 24 for the 15 mg/kg/day GWP42003-P Dose Level Compared with Placebo <sup>[1][2]</sup>
End point description: RSBQ is a caregiver-completed questionnaire that measures the frequency of current disease characteristics (45 items) in individuals with Rett Syndrome. Each item is rated on a 3-point scale (0-2); 0 indicating an item that is "not true as far as you know," 1 indicating an item is "somewhat or sometimes true," and 2 indicating an item that is "very true or often true." Higher scores represent greater severity. Except for item 31 ("Uses eye gaze to convey feelings, needs and wishes"), which is reverse-scored (0 indicating "very true or often true", 1 indicating "somewhat or sometimes true" and 2 indicating "not true as far as you know"). Analysis was conducted in members of the ITT Set, defined as all randomized subjects who received at least 1 dose of drug in the trial, and had Baseline efficacy data. CFB = Change from Baseline.	
End point type	Primary
End point timeframe: Baseline; Week 24	

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: Only descriptive statistical analysis was performed for this primary end point. The planned inferential statistical analysis was not carried out due to the limited sample size compared to that planned, because of the trial termination.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only the comparison between GWP42003-P 15 mg/kg group with placebo was evaluated in this primary end point.

End point values	15 mg/kg/day GWP42003-P	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9 <sup>[3]</sup>	10 <sup>[4]</sup>		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline, n=9, 10	45.9 (± 16.77)	50.0 (± 7.56)		
CFB at Week 24, n=7, 7	-12.1 (± 13.63)	-6.1 (± 7.22)		

Notes:

[3] - ITT Set. Subjects with non-missing data (n) were included for analysis.

[4] - ITT Set. Subjects with non-missing data (n) were included for analysis.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the Mean RSBQ Total Score at Week 24 for the 5 mg/kg/day GWP42003-P Dose Level Compared with Placebo

End point title	Change from Baseline in the Mean RSBQ Total Score at Week 24 for the 5 mg/kg/day GWP42003-P Dose Level Compared with Placebo <sup>[5]</sup>
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End point description:

RSBQ is a caregiver-completed questionnaire that measures the frequency of current disease characteristics (45 items) in individuals with Rett Syndrome. Each item is rated on a 3-point scale (0-2); 0 indicating an item that is "not true as far as you know," 1 indicating an item is "somewhat or sometimes true," and 2 indicating an item that is "very true or often true." Higher scores represent greater severity. Except for item 31 ("Uses eye gaze to convey feelings, needs and wishes"), which is reverse-scored (0 indicating "very true or often true", 1 indicating "somewhat or sometimes true" and 2 indicating "not true as far as you know"). CFB = Change from Baseline.

End point type	Secondary
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End point timeframe:

Baseline; Week 24

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only the comparison between GWP42003-P 5 mg/kg group with placebo was evaluated in this secondary end point.

End point values	5 mg/kg/day GWP42003-P	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 <sup>[6]</sup>	10 <sup>[7]</sup>		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline, n=10, 10	39.8 (± 12.80)	50.0 (± 7.56)		
CFB at Week 24, n=9, 7	0.4 (± 12.51)	-6.1 (± 7.22)		

Notes:

[6] - ITT Set. Subjects with non-missing data (n) were included for analysis.

[7] - ITT Set. Subjects with non-missing data (n) were included for analysis.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Clinical Global Impressions-Improvement (CGI-I) Score at Week 24

End point title	Mean Clinical Global Impressions-Improvement (CGI-I) Score at Week 24
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End point description:

CGI-I is a 7-point scale that requires the clinician to assess how much a subject's illness has improved or worsened relative to a Baseline state at the beginning of the intervention. This is rated as: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; or 7 = very much worse.

End point type	Secondary
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End point timeframe:

Week 24

End point values	5 mg/kg/day GWP42003-P	15 mg/kg/day GWP42003-P	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9 <sup>[8]</sup>	7 <sup>[9]</sup>	7 <sup>[10]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)	3.2 (± 1.20)	2.9 (± 1.07)	3.1 (± 0.38)	

Notes:

[8] - ITT Set. Subjects with non-missing data (n) were included for analysis.

[9] - ITT Set. Subjects with non-missing data (n) were included for analysis.

[10] - ITT Set. Subjects with non-missing data (n) were included for analysis.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Mean Clinician Global Impressions - Severity (CGI-S) Score at Week 24

End point title	Change from Baseline in Mean Clinician Global Impressions - Severity (CGI-S) Score at Week 24
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End point description:

CGI-S is a 7-point scale that requires the clinician to rate the severity of the subject's illness at the time of assessment relative to the clinician's experience with subjects who had the same diagnosis. This is rated as: 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; or 7 = extremely ill. CFB = Change from Baseline.

End point type	Secondary
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End point timeframe:

Baseline; Week 24

End point values	5 mg/kg/day GWP42003-P	15 mg/kg/day GWP42003-P	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10 <sup>[11]</sup>	9 <sup>[12]</sup>	10 <sup>[13]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline, n=10, 9, 10	4.3 (± 1.25)	4.2 (± 0.67)	4.4 (± 0.84)	
CFB at Week 24, n=9, 7, 7	-0.1 (± 0.33)	-0.1 (± 0.38)	0.0 (± 0.00)	

Notes:

[11] - ITT Set. Subjects with non-missing data (n) were included for analysis.

[12] - ITT Set. Subjects with non-missing data (n) were included for analysis.

[13] - ITT Set. Subjects with non-missing data (n) were included for analysis.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Mean RSBQ Subscale Scores at Week 24

End point title	Change from Baseline in Mean RSBQ Subscale Scores at Week 24
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End point description:

RSBQ is a caregiver-completed questionnaire that measures the frequency of current disease characteristics (45 items) in individuals with Rett Syndrome. Each item is rated on a 3-point scale (0-2); 0 indicating an item that is "not true as far as you know," 1 indicating an item is "somewhat or sometimes true," and 2 indicating an item that is "very true or often true." Higher scores represent greater severity. Except for item 31 ("Uses eye gaze to convey feelings, needs and wishes"), which is reverse-scored (0 indicating "very true or often true", 1 indicating "somewhat or sometimes true" and 2 indicating "not true as far as you know"). The 45-item RSBQ is comprised of 8 subscales: 1) general mood, 2) breathing problems, 3) hand behaviors, 4) face movements, 5) body rocking (BR)/expressionless face, 6) night-time behaviors, 7) anxiety/fear, 8) walking/standing. CFB = Change from Baseline.

End point type	Secondary
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End point timeframe:

Baseline; Week 24

End point values	5 mg/kg/day GWP42003-P	15 mg/kg/day GWP42003-P	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10 <sup>[14]</sup>	9 <sup>[15]</sup>	10 <sup>[16]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline General Mood Score, n=10, 9, 10	6.0 (± 3.65)	8.2 (± 4.58)	8.9 (± 3.14)	
CFB General Mood Score, n=9, 7, 7	-0.6 (± 2.70)	-4.9 (± 2.67)	-2.6 (± 2.57)	
Baseline Breathing Problems Score, n=10, 9, 10	4.7 (± 2.45)	5.0 (± 3.08)	5.0 (± 3.43)	
CFB Breathing Problems Score, n=9, 7, 7	0.2 (± 1.86)	-1.0 (± 1.53)	-0.3 (± 1.25)	
Baseline Hand Behaviors Score, n=10, 9, 10	7.8 (± 2.15)	7.6 (± 3.54)	9.1 (± 2.08)	

CFB Hand Behaviors Score, n=9, 7, 7	0.7 (± 2.24)	-0.9 (± 3.29)	0.1 (± 0.90)	
Baseline Face Movements Score, n=10, 9, 10	2.3 (± 2.45)	4.6 (± 2.13)	4.3 (± 2.21)	
CFB Face Movements Score, n=9, 7, 7	0.0 (± 1.12)	-1.4 (± 1.72)	-0.1 (± 1.07)	
Baseline BR/Expressionless Face Score, n=10, 9, 10	4.5 (± 2.59)	5.1 (± 1.96)	5.4 (± 2.59)	
CFB BR/Expressionless Face Score, n=9, 7, 7	0.6 (± 2.46)	-0.6 (± 1.13)	-0.1 (± 1.86)	
Baseline Night-time Behaviors Score, n=10, 9, 10	0.8 (± 1.14)	0.8 (± 0.97)	1.8 (± 1.69)	
CFB Night-time Behaviors Score, n=9, 7, 7	0.2 (± 0.97)	-0.1 (± 1.46)	-0.3 (± 1.11)	
Baseline Anxiety/Fear Score, n=10, 9, 10	4.0 (± 1.89)	4.6 (± 2.46)	5.1 (± 1.45)	
CFB Anxiety/Fear Score, n=9, 7, 7	-0.2 (± 1.92)	-1.3 (± 2.29)	-1.7 (± 0.95)	
Baseline Walking/Standing Score, n=10, 9, 10	2.7 (± 1.64)	2.1 (± 1.36)	2.9 (± 1.29)	
CFB Walking/Standing Score, n=9, 7, 7	0.9 (± 2.09)	0.0 (± 0.58)	0.1 (± 1.07)	

Notes:

[14] - ITT Set. Subjects with non-missing data (n) were included for analysis.

[15] - ITT Set. Subjects with non-missing data (n) were included for analysis.

[16] - ITT Set. Subjects with non-missing data (n) were included for analysis.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Mean 9-item Motor Behavioral Assessment (MBA-9) Total Score and Subscale scores at Week 24

End point title	Change from Baseline in Mean 9-item Motor Behavioral Assessment (MBA-9) Total Score and Subscale scores at Week 24
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End point description:

MBA-9 is derived from the full MBA scale (37 Rett syndrome symptoms) by selecting the items deemed amenable to change and which reflected areas of meaningful clinical change. The severity of current symptoms is rated by the investigator on a 5-point numerical scale; (0 = normal or never; 1 = mild or rare; 2 = moderate or occasional; 3 = marked or frequent; 4 = very severe or constant). The MBA-9 score is calculated by summing the scores of the individual items. The maximum score is 36; higher total scores represent greater severity. CFB = Change from Baseline.

End point type	Secondary
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End point timeframe:

Baseline; Week 24

End point values	5 mg/kg/day GWP42003-P	15 mg/kg/day GWP42003-P	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10 <sup>[17]</sup>	9 <sup>[18]</sup>	10 <sup>[19]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline Regression of Motor Skills, n=10, 9, 10	2.2 (± 1.23)	2.6 (± 0.88)	2.6 (± 0.84)	
CFB Regression of Motor Skills, n=9, 7, 7	0.3 (± 1.58)	-0.3 (± 0.49)	0.0 (± 0.58)	
Baseline Poor Eye/Social Contact, n=10, 9, 10	1.7 (± 0.82)	1.6 (± 1.01)	1.5 (± 0.97)	

CFB Poor Eye/Social Contact, n=9, 7, 7	0.0 (± 0.87)	-0.1 (± 0.69)	-0.9 (± 1.07)
Baseline Lack of Sustained Interest, n=10, 9, 10	1.8 (± 0.79)	2.1 (± 1.17)	1.5 (± 0.71)
Lack of Sustained Interest, n=9, 7, 7	0.0 (± 0.71)	-0.3 (± 1.11)	-0.1 (± 0.38)
Baseline DNR for Objects or People, n=10, 9, 10	2.0 (± 1.25)	1.9 (± 1.05)	2.3 (± 1.25)
CFB DNR for Objects or People, n=9, 7, 7	-0.4 (± 2.24)	-0.4 (± 0.98)	0.1 (± 1.21)
Baseline Chewing Difficulties, n=10, 9, 10	1.3 (± 1.34)	1.3 (± 0.50)	1.1 (± 0.74)
Chewing Difficulties, n=9, 7, 7	-0.2 (± 0.67)	0.0 (± 0.00)	0.4 (± 0.53)
Baseline Speech Disturbance, n=10, 9, 10	3.0 (± 0.47)	2.8 (± 0.83)	2.7 (± 0.48)
CFB Speech Disturbance, n=9, 7, 7	0.0 (± 0.00)	0.0 (± 0.58)	0.3 (± 0.49)
Baseline Hand Clumsiness, n=10, 9, 10	2.8 (± 1.14)	2.8 (± 1.56)	3.1 (± 1.10)
CFB Hand Clumsiness, n=9, 7, 7	-0.6 (± 1.33)	-0.4 (± 1.13)	0.0 (± 0.58)
Baseline Dysonia, n=10, 9, 10	1.0 (± 1.41)	1.2 (± 1.56)	1.0 (± 1.41)
CFB Dysonia, n=9, 7, 7	0.4 (± 1.42)	-0.1 (± 0.90)	0.1 (± 1.46)
Baseline Hypertonia/Rigidity, n=10, 9, 10	1.4 (± 1.51)	1.1 (± 1.45)	1.0 (± 1.41)
CFB Hypertonia/Rigidity, n=9, 7, 7	0.4 (± 0.73)	-0.1 (± 0.38)	0.0 (± 1.00)
Baseline MBA-9 Total Score, n=10, 9, 10	17.2 (± 5.81)	17.3 (± 6.78)	16.8 (± 5.96)
CFB MBA-9 Total Score, n=9, 7, 7	0.0 (± 4.87)	-1.9 (± 4.06)	0.0 (± 3.92)

Notes:

[17] - ITT Set. Subjects with non-missing data (n) were included for analysis.

[18] - ITT Set. Subjects with non-missing data (n) were included for analysis.

[19] - ITT Set. Subjects with non-missing data (n) were included for analysis.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Mean Children's Sleep Habits Questionnaire (CSHQ) Total Score and Subscale Scores at Week 24

End point title	Change from Baseline in Mean Children's Sleep Habits Questionnaire (CSHQ) Total Score and Subscale Scores at Week 24
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End point description:

The CSHQ is a caregiver-completed sleep screening instrument designed for school-aged children, including 33 items within 8 subscales reflecting the following sleep domains: 1) bedtime resistance, 2) sleep onset delay, 3) sleep duration, 4) sleep anxiety, 5) night wakings, 6) parasomnias, 7) sleep-disordered breathing, 8) daytime sleepiness. Each item is answered with 1 of 3 markers: "usually," for 5 or more times a week, "sometimes," for 2-4 times a week, and "rarely," for never or 1 time a week. Higher scores reflect more disturbed sleep behavior. CFB = Change from Baseline.

End point type	Secondary
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End point timeframe:

Baseline; Week 24

End point values	5 mg/kg/day GWP42003-P	15 mg/kg/day GWP42003-P	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10 <sup>[20]</sup>	9 <sup>[21]</sup>	10 <sup>[22]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline Total Score, n=10, 9, 10	49.8 (± 9.75)	46.7 (± 4.90)	49.4 (± 5.42)	
CFB Total Score, n=9, 7, 7	-1.6 (± 6.17)	-5.0 (± 6.14)	-3.7 (± 4.07)	
Baseline Bedtime resistance, n=10, 9, 10	9.2 (± 3.43)	7.3 (± 2.12)	7.0 (± 1.25)	
CFB Bed-time resistance, n=9, 7, 7	0.0 (± 1.00)	-0.4 (± 1.27)	-0.1 (± 1.68)	
Baseline Sleep onset delay, n=10, 9, 10	1.5 (± 0.71)	1.4 (± 0.53)	1.8 (± 0.79)	
CFB Sleep onset delay, n=9, 7, 7	0.1 (± 1.27)	-0.1 (± 0.69)	-0.6 (± 0.53)	
Baseline Sleep duration, n=10, 9, 10	4.7 (± 2.41)	3.4 (± 0.73)	4.5 (± 1.58)	
CFB Sleep duration, n=9, 7, 7	0.4 (± 1.13)	-0.3 (± 0.95)	-0.4 (± 1.72)	
Baseline Sleep anxiety, n=10, 9, 10	5.6 (± 1.65)	4.6 (± 0.73)	4.9 (± 1.10)	
CFB Sleep anxiety, n=9, 7, 7	-0.1 (± 0.78)	-0.1 (± 0.38)	0.0 (± 1.15)	
Baseline Night wakings, n=10, 9, 10	5.3 (± 2.36)	4.4 (± 1.33)	4.6 (± 1.43)	
CFB Night wakings, n=9, 7, 7	-0.4 (± 0.88)	-0.6 (± 1.40)	0.1 (± 0.69)	
Baseline Parasomnias, n=10, 9, 10	11.0 (± 1.49)	10.4 (± 1.42)	11.7 (± 2.63)	
CFB Parasomnias, n=9, 7, 7	-0.6 (± 1.51)	-1.1 (± 1.68)	-1.4 (± 2.30)	
Baseline Sleep disordered breathing, n=10, 9, 10	4.2 (± 1.69)	4.0 (± 1.22)	3.7 (± 1.06)	
CFB Sleep disordered breathing, n=9, 7, 7	-0.4 (± 1.74)	-0.9 (± 1.07)	-0.1 (± 0.38)	
Baseline Daytime sleepiness, n=10, 9, 10	11.6 (± 3.20)	13.2 (± 2.39)	13.7 (± 2.50)	
CFB Daytime sleepiness, n=9, 7, 7	-0.7 (± 3.64)	-1.4 (± 2.07)	-1.3 (± 2.56)	

Notes:

[20] - ITT Set. Subjects with non-missing data (n) were included for analysis.

[21] - ITT Set. Subjects with non-missing data (n) were included for analysis.

[22] - ITT Set. Subjects with non-missing data (n) were included for analysis.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to approximately 207 days

Adverse event reporting additional description:

Safety Analysis Set: Subjects who received at least 1 dose of IMP in the trial were included and analyzed according to the treatment received. One subject who was assigned to the placebo group received GWP42003-P 5 milligram (mg)/kilogram (kg). For safety analyses, this subject was assigned to the GWP42003-P 5 mg/kg.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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### Reporting groups

Reporting group title	5 mg/kg/day GWP42003-P
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Reporting group description:

Subjects received 5 mg/kg/day GWP42003-P, administered as 100 mg/milliliter (mL) oral solution twice daily (BID). One subject who was assigned to the placebo group received GWP42003-P 5 mg/kg. For safety analyses, this subject was assigned to the GWP42003-P 5 mg/kg group.

Reporting group title	Placebo
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Reporting group description:

Subjects received placebo oral solution matched to 5 or 15 mg/kg/day GWP42003-P, BID. One subject who was assigned to the placebo group received GWP42003-P 5 mg/kg. For safety analyses, this subject was assigned to the GWP42003-P 5 mg/kg group.

Reporting group title	15 mg/kg/day GWP42003-P
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Reporting group description:

Subjects received 15 mg/kg/day GWP42003-P, administered as 100 mg/mL oral solution BID.

Serious adverse events	5 mg/kg/day GWP42003-P	Placebo	15 mg/kg/day GWP42003-P
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 11 (18.18%)	1 / 9 (11.11%)	2 / 9 (22.22%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Dyskinesia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	5 mg/kg/day GWP42003-P	Placebo	15 mg/kg/day GWP42003-P
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 11 (81.82%)	7 / 9 (77.78%)	7 / 9 (77.78%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	2 / 9 (22.22%)
occurrences (all)	0	1	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Choking			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Hiccups			

subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Hyperventilation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Bruxism			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Dermatillomania			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	1 / 11 (9.09%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	1	2	0
Irritability			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Middle insomnia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Nervousness			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Sleep disorder			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Breath sounds abnormal			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Mean cell volume increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Sunburn			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Disturbance in attention			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Dizziness postural			

subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Drooling			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hyperreflexia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Lethargy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	3 / 9 (33.33%)
occurrences (all)	0	0	3
Seizure			
subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	2	1	0
Somnolence			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Eosinophilia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Macrocytosis			
subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Neutropenia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Constipation subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2	0 / 9 (0.00%) 0	2 / 9 (22.22%) 2
Faeces soft subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Tooth discolouration subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	2 / 9 (22.22%) 3
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 9 (11.11%) 1	1 / 9 (11.11%) 1
Skin discolouration subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Joint stiffness subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Scoliosis			

subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 11 (18.18%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Otitis media			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)	3 / 9 (33.33%)	0 / 9 (0.00%)
occurrences (all)	1	5	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	4	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Hypoglycaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Selenium deficiency			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2019	<ul style="list-style-type: none"><li>- Exclusion criteria were updated to exclude patients with moderate hepatic impairment; added clarification to investigational medicinal product (IMP) dosing instructions and compliance documentation and information collected on pharmacokinetic sample collection days; updated the list of prohibited therapies during the trial; and added clarifications to the statistical analysis and trial monitoring.</li><li>-Updated the exclusion criteria related to hepatic and cardiovascular functions, contraception and hypersensitivity to cannabinoids or excipients.</li><li>-Added additional time points to the safety assessments (pregnancy, electrocardiogram, clinical laboratory).</li><li>-Information on concomitant therapy and potential drug interactions and dose reduction of IMP were added.</li><li>-Minimum age was lowered from 4 years to 2 years in the inclusion criteria.</li><li>-Caregiver assessment of Rett symptoms (symptom diary) was added.</li></ul>
18 July 2019	<ul style="list-style-type: none"><li>- The protocol was updated to specify the Rett Syndrome Behaviour Questionnaire (RSBQ) as the primary end point, and the Clinical Global Impressions - Improvement (CGI-I) as the key secondary end point.</li><li>- Contraceptive measures were more precisely documented within the protocol, and aligned with the Clinical Trial Facilitation Group guideline.</li><li>- The protocol was updated to include a benefit-risk assessment concluding that the overall benefit-risk for the development of Cannabidiol oral solution in the Rett syndrome population is favorable.</li><li>- Clarification that methyl CpG binding protein 2 (MECP2) mutation must be pathogenic; removal of option to proceed with randomization without confirmation of mutation type; this was to ensure sites confirm the genetic mutation was pathogenic prior to randomization.</li><li>- Clarification on criteria requiring IMP discontinuation rather than study withdrawal, as patients/caregivers were encouraged to remain in the trial and continue to complete trial assessments/visits as per protocol even if IMP was discontinued.</li></ul>
07 July 2020	<ul style="list-style-type: none"><li>- Inclusion criteria were changed to allow the enrolment of males, the contraception requirements and tanner staging were updated for inclusion of males.</li><li>- Wording regarding IMP administration via gastrostomy or nasogastric feeding tube was updated in the inclusion criteria and the IMP administration sections to remove reference to specific tube materials and instead required a discussion with the medical monitor to confirm suitability of tubes being used.</li><li>- The number of sites expected to participate was increased to 35 from 25. The requirement of subject weight &lt;13 kg was updated to &lt;19 kg for the collection of blood sample at Visit 1/prior to Visit 1 for MECP2 mutation analysis and the permitted visit window for Visit 2 of +3 days was updated to +6 days from the scheduled visit date so that sufficient time was available for MECP2 mutation analysis results. Language related to meal at Visit 5 and telephone visits (Visits 3, 4 and 11) was updated. Informed consent procedure and training requirements were updated as a result of the change in policy with the Sponsor.</li><li>- A new section for special circumstances was included to detect cases of suspected or confirmed COVID-19 infection (or other significant communicable infectious diseases) within a year of Screening (Visit 1).</li><li>- Language updates were made to the reporting procedures for all AEs in relation to action taken with trial medication; to the trial monitoring procedure to reflect that monitoring might occur onsite or remotely; and to align with the GW Research Ltd publication policy.</li></ul>

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

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

This study was terminated early due to enrollment challenges and the COVID-19 pandemic. Numbers of subjects in each treatment groups were small, which precluded the planned formal statistical inferences and limited data interpretation.
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Notes: