Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Study of Diazoxide Choline Controlled-Release Tablet (DCCR) in Patients with Prader-Willi Syndrome

Summary

EudraCT number	2018-004215-50
Trial protocol	GB
Global end of trial date	09 June 2021

Results information

Result version number	v2 (current)
This version publication date	01 September 2023
First version publication date	29 March 2023
Version creation reason	• Correction of full data set Minor updates and clarifications.

Trial information

Trial identification

Sponsor protocol code	C601

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03440814
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Soleno Therapeutics UK Limited
Sponsor organisation address	Garden Cottage, Badgemore Park, Henley-on-Thames, United Kingdom, RG9 4NR
Public contact	Clinical Trial Information, Soleno Therapeutics UK Limited, 44 1491756023, soleno-uk@soleno.life
Scientific contact	Clinical Trial Information, Soleno Therapeutics UK Limited, 44 1491756022, C601ProjectManager@soleno.life

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	09 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 June 2021
Global end of trial reached?	Yes
Global end of trial date	09 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of diazoxide choline controlled release compared to placebo on hyperphagia in PWS subjects.

Protection of trial subjects:

IDMC (Data Safety Monitoring Board) met two times during study to review unblinded safety data.

Background therapy:

Subjects were titrated to a maintenance dose over a 2-6 week period depending on subjects' weight.

Evidence for comparator: -

Actual start date of recruitment	17 May 2018
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: 101
Country: Number of subjects enrolled	United Kingdom: 25
Worldwide total number of subjects	126
EEA total number of subjects	0

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)	60
Adolescents (12-17 years)	41
Adults (18-64 years)	25
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

People with PWS who met the eligibility criteria were enrolled / randomised. The first subject was screened in the US on 17May2018 and in the UK on 26Jun2019; all sites were either hospitals or academic medical centres.

Pre-assignment

Screening details:

181 subjects were screened, 158 were eligible and entered the two-week, single-blind placebo run-in period and 127 subjects were enrolled / randomised in the trial. 126 of the 127 subjects took any amount of study drug.

Period 1

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

Blinding implementation details:

Study team members were blinded to the randomised assignment. Study drug was also blinded. Placebo tablets matching the size, shape and colour of the respective DCCR tablet strengths were used.

Arms

Are arms mutually exclusive?	Yes
Arm title	DCCR

Arm description: -

Arm type	Experimental
Investigational medicinal product name	DCCR
Investigational medicinal product code	
Other name	Diazoxide choline controlled release, Diazoxide choline extended-release
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Participants with PWS were dosed dependent on their weight; 25mg, 75mg or 150mg DCCR tablets could be taken; DCCR was taken once daily. Tablets must be swallowed whole and should not be broken, crushed or chewed.

The target dose by weight(kg) was as follows:

Subjects weighing 20 to <30kg took 100mg DCCR/day
Subjects weighing equal to or greater than 30 to <40kg took 150mg DCCR/day
Subjects weighing equal to or greater than 40 to <65kg took 225mg DCCR/day
Subjects weighing equal to or greater than 65 to <100kg took 375mg DCCR/day
Subjects weighing equal to or greater than 100 to <135kg took 450mg DCCR/day

Subjects randomised to the DCCR treatment group were titrated every 2 weeks until the target dose was achieved.

Arm title	Placebo for DCCR

Arm description: -

Arm type	Placebo

Investigational medicinal product name	Placebo for DCCR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants with PWS were dosed dependent on their weight; 25mg, 75mg or 150mg placebo tablets could be taken; Placebo was taken once daily. Tablets must be swallowed whole and should not be broken, crushed or chewed.

The target dose by weight(kg) was as follows:

Subjects weighing 20 to <30kg took 100mg placebo/day
Subjects weighing equal to or greater than 30 to <40kg took 150mg placebo/day
Subjects weighing equal to or greater than 40 to <65kg took 225mg placebo/day
Subjects weighing equal to or greater than 65 to <100kg took 375mg placebo/day
Subjects weighing equal to or greater than 100 to <135kg took 450mg placebo/day

Subjects randomised to the placebo group were titrated on placebo, similar to the DCCR group.

Number of subjects in period 1	DCCR	Placebo for DCCR
Started	84	42
Completed	79	41
Not completed	5	1
Adverse event, not serious	-	1
Adverse event, non-fatal	2	-
Consent withdrawn by parent/legal guardian	1	-
Lost to follow-up	2	-

Baseline characteristics

Reporting groups

Reporting group title	Double blind treatment period

Reporting group description:

The reporting group included 126 subjects who received at least one dose of study medication.

Reporting group values	Double blind treatment period	Total	
Number of subjects	126	126	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	60	60	
Adolescents (12-17 years)	41	41	
Adults (18-64 years)	25	25	
From 65-84 years	0	0	
85 years and over	0	0	
Age	0	0	
Age continuous Units: years			
arithmetic mean	13.4		
full range (min-max)	4 to 44	-	
Gender categorical Units: Subjects			
Female	70	70	
Male	56	56	

Subject analysis sets

Subject analysis set title	Intent-to-treat (ITT) population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population includes all randomised subjects who had a Baseline HQ-CT value and at least one post-Baseline HQ-CT value.

Subject analysis set title	Intent to treat (ITT) population - Pre-COVID Analysis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The pre-COVID analysis population consisted of all subjects who had at least one post-baseline assessment of HQ-CT prior to March 1, 2020 when a national emergency was declared in the US as a result of the COVID-19 pandemic.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population includes all randomised subjects who received at least one dose of study drug.

Reporting group values	Intent-to-treat (ITT) population	Intent to treat (ITT) population - Pre-COVID Analysis	Safety population
Number of subjects	124	124	126
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	58	58	60
Adolescents (12-17 years)	41	41	41
Adults (18-64 years)	25	25	25
From 65-84 years	0	0	0
85 years and over	0	0	0
Age	0	0	0
Age continuous Units: years			
arithmetic mean	13.5	13.5	13.4
full range (min-max)	4 to 44	4 to 44	4 to 44
Gender categorical Units: Subjects			
Female	69	69	70
Male	55	55	56

End points

End points reporting groups

Reporting group title	DCCR
Reporting group description: -	
Reporting group title	Placebo for DCCR
Reporting group description: -	
Subject analysis set title	Intent-to-treat (ITT) population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population includes all randomised subjects who had a Baseline HQ-CT value and at least one post-Baseline HQ-CT value.	
Subject analysis set title	Intent to treat (ITT) population - Pre-COVID Analysis
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The pre-COVID analysis population consisted of all subjects who had at least one post-baseline assessment of HQ-CT prior to March 1, 2020 when a national emergency was declared in the US as a result of the COVID-19 pandemic.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population includes all randomised subjects who received at least one dose of study drug.	

Primary: Hyperphagia Questionnaire (HQ-CT) Change from Baseline at Visit 7 (Week 13)

End point title	Hyperphagia Questionnaire (HQ-CT) Change from Baseline at Visit 7 (Week 13)
End point description:	
Hyperphagia-related behaviors were assessed by the validated hyperphagia questionnaire for clinical trials (HQ-CT), an instrument designed to measure symptoms of food related preoccupations and behaviors that was completed by the caregiver. The HQ-CT consists of nine items with responses ranging from 0–4 units each (possible total score range: 0−36). The HQ-CT was assessed at Screening, Baseline (Visit 2), and approximately every 4 weeks post-dose at Week 4, Week 8, and Week 13. A decrease in score from baseline represented improvement.	
End point type	Primary
End point timeframe:	
Baseline to Visit 7 (Week 13)	

End point values	DCCR	Placebo for DCCR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	42		
Units: HQ-CT Score				
least squares mean (standard error)	-5.94 (± 0.879)	-4.27 (± 1.145)		

Statistical analyses

Statistical analysis title	Primary endpoint - HQ-CT

Statistical analysis description:

The primary endpoint (change from Baseline at Visit 7 (Week 13) in the HQ-CT Total Score) was analysed using a linear mixed model for repeated measurements in the ITT Population. All available data from each subject was used, with no imputation of missing data.

Comparison groups	DCCR v Placebo for DCCR
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1983 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.24
upper limit	0.89
Variability estimate	Standard error of the mean
Dispersion value	1.294

Notes:

[1] - The primary endpoint was analysed using a linear mixed model for repeated measurements in the ITT Population. All available data from each subject was used, with no imputation of missing data.

Secondary: Clinical Global Impression of Improvement (CGI-I) at Visit 7 (Week 13)

End point title	Clinical Global Impression of Improvement (CGI-I) at Visit 7 (Week 13)

End point description:

The Clinical Global Impression of Improvement (CGI-I) is a single statement designed to assess the Investigator's overall perception of change in the subject's condition across the course of the clinical trial. The Investigator provided a response to "Compared to the subject's condition at enrolment, the subject's condition is:" by rating the subject's behavior using a 7-point response scale: Very much improved, Much improved, Minimally improved, No change, Minimally worse, Much worse, and Very much worse. The Investigator only took into account the subject's PWS condition.

End point type	Secondary

End point timeframe:

At Visit 7 (Week 13)

End point values	DCCR	Placebo for DCCR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	42		
Units: Participants				
Very Much Improved	0	0		
Much Improved	5	0		
Minimally Improved	25	2		
No Change	41	37		
Minimally Worse	11	3		
Much Worse	0	0		
Very Much Worse	0	0		

Statistical analyses

Statistical analysis title	CGI-I at Visit 7 (Week 13)

Statistical analysis description:

The Clinical Global Impression of Improvement was compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) mean score test with modified ridit scores, stratified by the randomisation stratification variables.

Comparison groups	DCCR v Placebo for DCCR
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0294 [3]
Method	Cochran-Mantel-Haenszel

Notes:

[2] - Distribution difference

[3] - The Clinical Global Impression of Improvement was compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) mean score test with modified ridit scores, stratified by the randomisation stratification variables.

Secondary: Caregiver Global Impression of Change (GI-C) at Visit 7 (Week 13)

End point title	Caregiver Global Impression of Change (GI-C) at Visit 7 (Week 13)

End point description:

The Caregiver Global Impression of Change (GI-C) is a single statement designed to assess the caregiver's overall perception of change in the subject across the course of the clinical trial. The caregiver provided a response to "Please choose the response below that best describes the overall change in the person's PWS since they started taking the study medication" using a 7-point graded response scale: Very much better, Moderately better, A little better, No change, A little worse, Moderately worse, and Very much worse.

End point type	Secondary

End point timeframe:

At Visit 7 (Week 13)

End point values	DCCR	Placebo for DCCR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	42		
Units: Participants				
Very Much Improved	4	1		
Much Improved	6	3		
Minimally Improved	22	8		
No Change	39	20		
Minimally Worse	6	5		
Much Worse	4	3		
Very Much Worse	1	2		

Statistical analyses

Statistical analysis title	Caregiver GI-C at Visit 7 (Week 13)

Statistical analysis description:

Caregiver Global Impression of Change was compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) mean score test with modified ridit scores, stratified by the randomisation stratification variables.

Comparison groups	DCCR v Placebo for DCCR
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4089 [4]
Method	Cochran-Mantel-Haenszel

Notes:

[4] - Caregiver Global Impression of Change was compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) mean score test with modified ridit scores, stratified by the randomisation stratification variables.

Secondary: Change in Fat Mass (kg) from Baseline at Visit 7 (Week 13)

End point title	Change in Fat Mass (kg) from Baseline at Visit 7 (Week 13)

End point description:

Whole body scans were performed. Reports included a breakdown of the following regions: left arm, right arm, trunk, left leg, right leg, and head. Each region was evaluated for body fat mass (g).

End point type	Secondary

End point timeframe:

Baseline to Visit 7 (Week 13)

End point values	DCCR	Placebo for DCCR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	42		
Units: Body Fat Mass (kg)				
least squares mean (standard error)	-0.80 (± 0.356)	0.25 (± 0.444)		

Statistical analyses

Statistical analysis title	Change in Fat Mass (kg)

Statistical analysis description:

LSMeans are from an analysis of covariance (ANCOVA) model with the change from Baseline at Visit 7 (Week 13) as the response, Baseline value as covariate, and randomisation stratification variables (as randomised) as factors.

Comparison groups	DCCR v Placebo for DCCR

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0225 [5]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.95
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	0.458

Notes:

[5] - LSMeans are from an analysis of covariance (ANCOVA) model with the change from Baseline at Visit 7 (Week 13) as the response, Baseline value as covariate, and randomisation stratification variables (as randomised) as factors.

Post-hoc: Hyperphagia Questionnaire (HQ-CT) Change from Baseline at Visit 7 (Week 13) – Pre-COVID Analysis

End point title	Hyperphagia Questionnaire (HQ-CT) Change from Baseline at Visit 7 (Week 13) – Pre-COVID Analysis

End point description:

Hyperphagia-related behaviors were assessed by the validated hyperphagia questionnaire for clinical trials (HQ-CT), an instrument designed to measure symptoms of food related preoccupations and behaviors that was completed by the caregiver. The HQ-CT consists of nine items with responses ranging from 0–4 units each (possible total score range: 0−36). The HQ-CT was assessed at Screening, Baseline (Visit 2), and approximately every 4 weeks post-dose at Week 4, Week 8, and Week 13. A decrease in score from baseline represented improvement.

ITT Population - pre-COVID analysis - 01Mar2020 Cutoff.

End point type	Post-hoc

End point timeframe:

Baseline to Visit 7 (Week 13)

End point values	DCCR	Placebo for DCCR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	42		
Units: HQ-CT Score				
least squares mean (standard error)	-6.64 (± 1.001)	-3.51 (± 1.278)		

Statistical analyses

Statistical analysis title	Primary endpoint HQ-CT - Pre-COVID analysis

Statistical analysis description:

Pre-COVID Analysis population consisted of all subjects who had at least one post-baseline assessment of HQ-CT prior to March 1, 2020, when a national emergency was declared in the US as a result of the COVID-19 pandemic.

The primary endpoint (change in HQ-CT score from Baseline at Visit 7 (Week 13)) was analysed using a linear mixed model for repeated measurements in the Pre-COVID Analysis. All available data collected before the March 1, 2020 cutoff from each subject were included.

Comparison groups	DCCR v Placebo for DCCR
Number of subjects included in analysis	124
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0369 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.06
upper limit	-0.19
Variability estimate	Standard error of the mean
Dispersion value	1.481

Notes:

[6] - The primary endpoint was analysed using a mixed model for repeated measurements (MMRM) in Pre-COVID Analysis. All available data collected before the March 1, 2020 cutoff were used, with no imputation of missing data.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to Visit 7 (Week 13)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	DCCR

Reporting group description:

Participants with PWS were dosed dependent on their weight; 25mg, 75mg or 150mg DCCR tablets could be taken; DCCR was taken daily. Tablets must be swallowed whole and should not be broken, crushed or chewed.

The target dose by weight (kg) was as follows:

Subjects weighing 20 to < 30 kg took 100mg DCCR/day
Subjects weighing ≥ 30 to < 40 took 150mg DCCR/day
Subjects weighing ≥ 40 to < 65 took 225mg DCCR/day
Subjects weighing ≥ 65 to < 100 took 375mg DCCR/day
Subjects weighing ≥ 100 to < 135 took 450mg DCCR/day

Subjects randomised to the DCCR treatment group were titrated every 2 weeks until the target dose was achieved

Reporting group title	Placebo for DCCR

Reporting group description:

Participants with PWS were dosed dependent on their weight; 25mg, 75mg or 150mg placebo for DCCR tablets could be taken; Placebo was taken daily. Tablets must be swallowed whole and should not be broken, crushed or chewed.

The target dose by weight (kg) was as follows:

Subjects weighing 20 to < 30 kg took 100mg placebo for DCCR/day
Subjects weighing ≥ 30 to < 40 took 150mg placebo for DCCR/day
Subjects weighing ≥ 40 to < 65 took 225mg placebo for DCCR/day
Subjects weighing ≥ 65 to < 100 took 375mg placebo for DCCR/day
Subjects weighing ≥ 100 to < 135 took 450mg placebo for DCCR/day

Subjects randomised to the Placebo group were titrated on placebo, similar to the DCCR group

Serious adverse events	DCCR	Placebo for DCCR	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 84 (7.14%)	0 / 42 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Oedema peripheral			

subjects affected / exposed	1 / 84 (1.19%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	1 / 84 (1.19%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 84 (1.19%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 84 (1.19%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 84 (1.19%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aggression			
subjects affected / exposed	1 / 84 (1.19%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 84 (2.38%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 84 (1.19%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 84 (1.19%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	DCCR	Placebo for DCCR	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 84 (82.14%)	31 / 42 (73.81%)	
Investigations			
Blood glucose increased			
subjects affected / exposed	5 / 84 (5.95%)	2 / 42 (4.76%)	
occurrences (all)	5	2	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 84 (5.95%)	6 / 42 (14.29%)	
occurrences (all)	5	14	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	16 / 84 (19.05%)	4 / 42 (9.52%)	
occurrences (all)	28	4	
Pyrexia			
subjects affected / exposed	5 / 84 (5.95%)	0 / 42 (0.00%)	
occurrences (all)	6	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 84 (1.19%)	4 / 42 (9.52%)	
occurrences (all)	1	4	
Abdominal pain			
subjects affected / exposed	1 / 84 (1.19%)	3 / 42 (7.14%)	
occurrences (all)	1	5	
Skin and subcutaneous tissue disorders			

Hypertrichosis			
subjects affected / exposed	30 / 84 (35.71%)	6 / 42 (14.29%)	
occurrences (all)	32	6	
Hirsutism			
subjects affected / exposed	6 / 84 (7.14%)	3 / 42 (7.14%)	
occurrences (all)	8	6	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	9 / 84 (10.71%)	5 / 42 (11.90%)	
occurrences (all)	9	7	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	10 / 84 (11.90%)	0 / 42 (0.00%)	
occurrences (all)	10	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2018	This study was initiated globally as Protocol Amendment 1
19 July 2018	Revised/updated study objectives/endpoints and randomisation exclusion criteria. Added all PWS Profile Questionnaire domains and updated response scales, C-SSRS and DBC-2P. Modified inclusion criteria to include participants who are 4 years and older. Discontinuation id the study section was updated to include the timing of the DSMB's review of the unblinded safety data ad to define stopping criteria for the study. Modified exclusion criterion to exclude participants with signs suggestive of a thromboembolic event. HbA1c cutoff for entry moved from a screening entry criterion to an randomisation entry criterion. Removed requirement for blood pressure at Visit 2 since they would have to meet screening entry criterion prior to this visit. Safety parameters (laboratory and physical exam) updated for clarity and completeness.
12 November 2018	Revised/updated study objectives/endpoints. Added option to expand study to include clinical sites in Europe. Revised inclusion/exclusion to clarify acceptable genetic testing methods to confirm PWS diagnosis; required caregivers to be able to communicate with investigator (not required to be in English); exclude participants from entering data on non-interventional databases. Updated visit windows. Allowed for designation of a caregiver for completion of caregiver-completed questionnaires. Updated DNA sample collection to include blood sample in the event the saliva sample was insufficient to be analysed. DXA clarified to identify body regions to be included in body composition analysis. During run-in period, allowed weight band I participants to take only 1x75mg placebo tablet and did not require them to take 1x150mg placebo tablet. Clarified dosing instructions to ensure that study medication should be taken with a beverage that is not metabolised by CYP450 1A2 or 3A4. Added section on Home Health Nurse Visit.
26 April 2019	Revised/updated study inclusion/exclusion criteria. Added weight band 0 to allow enrolment of participants weighting 20 to <30kg; changes made throughout the protocol to incorporate this change. Medications known to prolong the QTc interval (Refer to QTDrugs List on https://crediblemeds.org/heathcare-providers/), except citalopram and synthetic steroids (i.e. oral, IM or IV) for > 7 days.
11 June 2019	Added additional ECG approximately 18-24 hours after first dose of DCCR or placebo if participant was taking citalopram or escitalopram.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

01 March 2020	While much of the study was conducted and completed prior to the onset of the COVID-19 pandemic and all subjects were enrolled and had baseline visits prior to the pandemic, a subset of subjects needed to complete some of their visits after the onset of the pandemic. The conduct of the study changed during the pandemic, with a number of study visits transitioning to telemedicine and/or home health nurse visits and in some cases, some procedures at some in-clinic visits could not be completed (for example DXA). In addition, the COVID-19 pandemic forced numerous restrictions on normal activities and often involved significant disruptions, changes in routine and schedules. Generally, this had a negative impact on both the subject, the caregiver, and the family, but in some cases, people with PWS responded positively to these changes. The pandemic therefore had a substantially adverse but inconsistent effect on the study conduct and results, particularly for subjective endpoints that relied on caregiver completed questionnaires (https://pubmed.ncbi.nlm.nih.gov/32515992/). Pandemic related effects on the subject or caregiver did not tend to impact objective endpoints, but these endpoints were impacted by the ability to obtain the data for analysis due to the shift to telemedicine or home health visits or due to limitations during an in-clinic visit. For this reason, the ITT population - Pre-COVID Analysis includes all data through	09 June 2021

Notes:

Limitations and caveats

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

All subjects were enrolled and had baseline visits prior to the COVID-19 pandemic. Additional information is provided in the section on Interruptions.

Notes: